Recurrent Hospitalization Among Patients With Atrial Fibrillation Undergoing Intracoronary Stenting Treated With 2 Treatment Strategies of Rivaroxaban or a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy

Recurrent Hospitalization Among Patients With Atrial Fibrillation Undergoing Intracoronary Stenting Treated With 2 Treatment Strategies of Rivaroxaban or a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy

BACKGROUND: Patients with atrial fibrillation who undergo intracoronary stenting traditionally are treated with a vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT), yet this treatment leads to high risks of bleeding. We hypothesized that a regimen of rivaroxaban plus a $P2Y_{12}$ inhibitor monotherapy or rivaroxaban plus DAPT could reduce bleeding and thereby have a favorable impact on all-cause mortality and the need for rehospitalization.

METHODS: Stented subjects with nonvalvular atrial fibrillation (n=2124) were randomized 1:1:1 to administration of reduced-dose rivaroxaban 15 mg daily plus a $P2Y_{12}$ inhibitor for 12 months (group 1); rivaroxaban 2.5 mg twice daily with stratification to a prespecified duration of DAPT of 1, 6, or 12 months (group 2); or the reference arm of dose-adjusted VKA daily with a similar DAPT stratification (group 3). The present post hoc analysis assessed the end point of all-cause mortality or recurrent hospitalization for an adverse event, which was further classified as the result of bleeding, a cardiovascular, or another cause blinded to treatment assignment.

RESULTS: The risk of all-cause mortality or recurrent hospitalization was 34.9% in group 1 (hazard ratio=0.79; 95% confidence interval, 0.66–0.94; *P*=0.008 versus group 3; number needed to treat=15), 31.9% in group 2 (hazard ratio=0.75; 95% confidence interval, 0.62–0.90; *P*=0.002 versus group 3; number needed to treat=10), and 41.9% in group 3 (VKA+DAPT). Both all-cause death plus hospitalization potentially resulting from bleeding (group 1=8.6% [*P*=0.032 versus group 3], group 2=8.0% [*P*=0.012 versus group 3], and group 3=12.4%) and all-cause death plus rehospitalization potentially resulting from a cardiovascular cause (group 1=21.4% [*P*=0.001 versus group 3], group 2=21.7% [*P*=0.011 versus group 3], and group 3=29.3%) were reduced in the rivaroxaban arms compared with the VKA arm, but other forms of rehospitalization were not.

CONCLUSIONS: Among patients with atrial fibrillation undergoing intracoronary stenting, administration of either rivaroxaban 15 mg daily plus $P2Y_{12}$ inhibitor monotherapy or 2.5 mg rivaroxaban twice daily plus DAPT was associated with a reduced risk of all-cause mortality or recurrent hospitalization for adverse events compared with standard-of-care VKA plus DAPT.

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Clinical Perspective

What Is New?

- Coronary stent patients with atrial fibrillation who are managed with triple therapy (vitamin K antagonist+dual antiplatelet therapy) face a high risk of bleeding. This substudy of the PIONEER trial (An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) demonstrates that either rivaroxaban 15 mg daily plus $P2Y_{12}$ inhibitor monotherapy or rivaroxaban 2.5 mg twice daily plus dual antiplatelet therapy is associated with a reduced risk of all-cause mortality or recurrent hospitalization for adverse events compared with standard-of-care vitamin K antagonist plus dual antiplatelet therapy.

What Are the Clinical Implications?

- Rehospitalizations potentially attributable to either bleeding or cardiovascular events were reduced with both rivaroxaban strategies.

Approximately 5% to 8% of patients undergoing coronary stent implantation also have atrial fibrillation (AF).[1–3] Among patients undergoing first-generation stent implantation, dual antiplatelet therapy (DAPT) is superior to vitamin K antagonist (VKA),[4] but among patients with AF, VKA is superior to DAPT in reducing the risk of ischemic stroke.[5] As a result, a common practice has been to combine DAPT and VKA to manage patients who have both a stent and AF.[6] Unfortunately, this strategy, often referred to as triple therapy, has been associated with major bleeding rates of 4% to 12% over the course of the first year of treatment.[7]

The primary results of the PIONEER study (An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) demonstrated that among subjects with AF undergoing intracoronary stent placement, administration of either rivaroxaban 15 mg daily plus $P2Y_{12}$ monotherapy for 1 year or rivaroxaban 2.5 mg twice daily plus 1, 6, or 12 months of DAPT at physician discretion significantly reduced the risk of clinically significant bleeding (TIMI [Thrombolysis in Myocardial Infarction] major+TIMI minor+bleeding requiring medical attention) compared with the current standard-of-care VKA plus 1, 6, or 12 months of DAPT with comparable efficacy, although the confidence intervals (CIs) were broad for efficacy.[8] We hypothesized that a significant reduction in bleeding with favorable trends in overall efficacy would also be associated with a significant reduction in all-cause mortality or recurrent hospitalization.

METHODS

Study Oversight

The executive committee, in conjunction with the sponsor, designed the study. All statistical analyses were performed by the PERFUSE (Perfusion Use in Stroke Evaluation Study) group using a copy of the Study Data Tabulation Model database. The academic members of the executive committee drafted the manuscript and made all revisions. Both national and institutional regulatory agencies and ethics committees approved the study. An independent data and safety monitoring board monitored the scientific integrity and the safety of the trial.

Study Population

Details of the trial design have been published previously.[9] In brief, the trial enrolled men and women >18 years of age with paroxysmal, persistent, or permanent nonvalvular AF who underwent percutaneous coronary intervention with stent placement. Major exclusion criteria included clinically significant bleeding within the past 12 months, a creatinine clearance <30 mL/min, anemia of unknown cause with a hemoglobin <10 g/dL, significant gastrointestinal bleeding within the past 12 months or any condition known to increase the risk of bleeding, a prior stroke or transient ischemic attack, stent placement during the index hospitalization for in-stent restenosis, and stent thrombosis during the index hospitalization. All subjects provided written informed consent.

Study Protocol and Treatment Strategies

Subjects were randomized within 72 hours of sheath removal once the international normalized ratio was ≤ 2.5. The responsible clinician prespecified the intended duration of DAPT (1, 6, or 12 months) and the intended $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) before randomization. Subjects were randomized in a 1:1:1 fashion to rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment [creatinine clearance 30–50 mL/min]) once daily plus background single antiplatelet therapy with clopidogrel 75 mg once daily (or ticagrelor 90 mg twice daily or prasugrel 10 mg once daily in up to 15% of subjects per group) for 12 months (although aspirin could be administered up to 24 hours before the first dose of study drug, it was to be withheld after randomization; group 1); rivaroxaban 2.5 mg twice daily plus background DAPT with low-dose aspirin (75–100 mg/d) plus clopidogrel 75 mg once daily (or ticagrelor 90 mg twice daily or prasugrel 10 mg once daily in up to 15% of subjects per group) for a prespecified duration of either 12 months or for 1 or 6 months followed by rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low-dose aspirin (75–100 mg; group 2); or traditional triple therapy with dose-adjusted VKA once daily to achieve a target international normalized ratio of 2.0 to 3.0 plus background DAPT with low-dose aspirin (75–100 mg/d) plus clopidogrel 75 mg once daily (or ticagrelor 90 mg twice daily or prasugrel 10 mg once daily in up to 15% of subjects per group) for a prespecified duration of either 12

months or for 1 or 6 months followed by dose-adjusted VKA once daily (target international normalized ratio, 2.0–3.0) plus background single antiplatelet therapy with low-dose aspirin (75–100 mg; group 3).

End Points

The primary end point of the substudy was the occurrence of all-cause death or rehospitalization for an adverse event. Adverse events were defined according to the International Conference on Harmonization guidelines. Study investigators were responsible for reporting all adverse events and indicating the seriousness of the event, as well as whether the event resulted in inpatient hospitalization. Those adverse events that resulted in hospitalization are included in this analysis. Two physicians (C.M.G. and G.C.) blinded to study drug assignment were provided with a list of adverse event terms associated with rehospitalization. All adverse events were classified as potentially attributable to bleeding, cardiovascular causes, or other causes through consensus. All adverse event terms, the number of events per term, and their categorization are shown in Table I in the online-only Data Supplement).

Statistical Analysis

SAS version 9.4 was used to perform all statistical analyses. All patients who received at least 1 dose of the study drug were included in the analysis; subjects were analyzed on an as-treated basis; and for the primary analysis, the data were pooled across all strata of DAPT duration (1, 6, 12 months) as prespecified. The cumulative percentages of all deaths and rehospitalizations for an adverse event observed from the time of the first study drug was first administered up to 2 days after discontinuation of the study drug were calculated. Two specific pairwise comparisons were made simultaneously (group 1 versus 3 and group 2 versus 3) with no adjustment to the type I error rate of 0.05. A Cox proportional hazard model was used to compare the time from administration of the first dose of study drug to the first occurrence any cause of death or hospitalization for an adverse event with treatment group as a covariate to provide a point estimate (hazard ratio [HR]) and 2-sided 95% CI. Cumulative event rates were summarized at 360 days with the Kaplan-Meier method. The Wei-Lin-Weissfeld method was used to calculate unadjusted HRs and 95% CIs for the multiple event analysis.[10] The Wei-Lin-Weissfeld method uses a semiparametric marginal Cox distribution and takes into account all multiple events of interest that a subject has during the study versus a traditional time to first event analysis. Because of the nonindependent nature of these data, sandwich variance estimation was used. Six subjects from 1 site (n=4 in the rivaroxaban groups versus n=2 in the VKA group) were excluded from all analyses because of violations of Good Clinical Practice guidelines before unblinding. A value of $P<0.05$ was considered statistically significant. This study was a nonprespecified post hoc analysis.

RESULTS

From May 10, 2013, through July 30, 2015, a total of 2124 subjects were randomized. The baseline characteristics of the subjects were well matched, as reported

Table 1. Baseline Characteristics

Characteristic	Group 1, Rivaroxaban+ $P2Y_{12}$ (n=709)	Group 2, Rivaroxaban+ DAPT (n=709)	Group 3, VKA+DAPT (n=706)
Age, mean±SD, y	70.4±9.1	70.0±9.1	69.9±8.7
≥65, n (%)	523 (73.8)	516 (72.8)	526 (74.5)
≥75, n (%)	254 (35.8)	245 (34.6)	230 (32.6)
Female sex, n (%)	181 (25.5)	174 (24.5)	188 (26.6)
Race,* n (%)			
White	662 (93.4)	671 (94.6)	664 (94.1)
Black	7 (1.0)	3 (0.4)	1 (0.1)
Asian	25 (3.5)	28 (4.0)	33 (4.7)
American Indian or Alaska Native	1 (0.1)	0 (0.0)	0 (0.0)
Other or unknown	14 (2.0)	7 (1.0)	8 (1.1)
Active smokers, n (%)	37 (5.2)	56 (7.9)	48 (6.8)
Creatinine clearance, mL/min			
Mean±SD	78.3±31.3	77.5±31.8	80.7±30.0
<60–≥30, n (%)	194 (28.8)	196 (28.8)	175 (26.2)
<30, n (%)	8 (1.2)	7 (1.0)	2 (0.3)
$P2Y_{12}$ inhibitor at baseline, n (%)			
Clopidogrel	660 (93.1)	664 (93.7)	680 (96.3)
Prasugrel	12 (1.7)	11 (1.6)	5 (0.7)
Ticagrelor	37 (5.2)	34 (4.8)	21 (3.0)
Type of index event, n (%)			
NSTEMI	130 (18.5)	129 (18.4)	123 (17.8)
STEMI	86 (12.3)	97 (13.8)	74 (10.7)
Unstable angina	145 (20.7)	148 (21.1)	164 (23.7)
Stable angina	340 (48.5)	329 (46.8)	330 (47.8)
Type of stent, n (%)			
Drug-eluting stent	464 (65.4)	471 (66.8)	468 (66.5)
Bare metal stent	231 (32.6)	220 (31.2)	224 (31.8)
Drug-eluting and bare metal stents	14 (2.0)	14 (2.0)	12 (1.7)
Type of AF, n (%)			
Persistent	146 (20.6)	146 (20.6)	149 (21.1)
Permanent	262 (37.0)	238 (33.6)	243 (34.5)
Paroxysmal	300 (42.4)	325 (45.8)	313 (44.4)
CHA_2DS_2-VASc risk of stroke, n (%)			
0	11 (1.6)	10 (1.4)	7 (1.0)
1	66 (9.3)	65 (9.2)	44 (6.2)
2	112 (15.8)	93 (13.1)	96 (13.6)

(*Continued*)

Table 1. Continued

Characteristic	Group 1, Rivaroxaban+ $P2Y_{12}$ (n=709)	Group 2, Rivaroxaban+ DAPT (n=709)	Group 3, VKA+DAPT (n=706)
3	125 (17.6)	122 (17.2)	148 (21.0)
4	138 (19.5)	153 (21.6)	174 (24.7)
5	140 (19.8)	163 (23.0)	125 (17.7)
6	93 (13.1)	85 (12.0)	91 (12.9)
7	24 (3.4)	18 (2.5)	21 (3.0)

AF indicates atrial fibrillation; DAPT, dual antiplatelet therapy; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and VKA, vitamin K antagonist. There were no significant differences among the 3 groups. Numbers are based on all randomized subjects and available data. Pairwise comparisons were calculated with the χ^2 test of independence for categorical variables and independent-samples *t* test for continuous variables.

*Race was self-reported.

in the primary publication[8] (Table 1 and Table II in the online-only Data Supplement). The median age was 71 years (interquartile range, 64–77 years), and 25.6% of subjects were women. The median $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were 2, 4, and 3, respectively.[8] The time in therapeutic range for the internationalized normalized ratio was 65% and did not vary by region.[8] No patients were lost to follow-up, and the ascertainment of all-cause death was 100% complete in this trial.[8]

The risk of all-cause mortality or recurrent hospitalization was 34.9% in group 1 (rivaroxaban 15 mg once daily+$P2Y_{12}$ inhibitor; HR= 0.79; 95% CI, 0.66–0.94; *P*=0.008 versus group 3 [VKA+DAPT]; number needed to treat=15), 31.9% in group 2 (rivaroxaban 2.5 mg twice daily+DAPT; HR=0.75; 95% CI, 0.62–0.90; *P*=0.002 versus group 3 [VKA+DAPT]; number needed to treat=10), and 41.9% in group 3 (reference group of VKA+DAPT; Table 2 and Figure 1). No significant interaction terms were found in subgroup analyses (Figures I and II in the online-only Data Supplement), including duration of DAPT. Both all-cause death plus hospitalization potentially for bleeding (group 1=8.6% [*P*=0.032 versus group 3], group 2=8.0% [*P*=0.012 versus group 3], and group 3=12.4%) and all-cause death plus rehospitalization potentially for a cardiovascular cause (group 1=21.4% [*P*=0.001 versus group 3], group 2=21.7% [*P*=0.011 versus group 3], and group 3=29.3%) were reduced in the rivaroxaban arms compared with the VKA arm. No reductions were seen for either rivaroxaban arm compared with the VKA arm for other causes of rehospitalization or for all-cause death (Table 2).

The rate of all-cause rehospitalization was 34.1% in group 1 (rivaroxaban 15 mg once daily+$P2Y_{12}$ inhibitor; HR=0.77; 95% CI, 0.65–0.92; *P*=0.005 versus group 3 [VKA+DAPT]), 31.2% in group 2 (rivaroxaban 2.5 twice daily+DAPT; HR=0.74; 95% CI, 0.61–0.88; *P*=0.001 versus group 3 [VKA+ DAPT]), and 41.5% in group 3 (reference arm of VKA+DAPT; Table 3 and Figure 2). The relative reduction in recurrent hospitalization was greater for bleeding events, but the absolute reduction in recurrent hospitalization was greater for cardiovascular events (Table 3 and Figure 3). There were no significant interaction terms in the assessment of subgroups, including DAPT duration (Figures III and IV in the online-only Data Supplement). Although the above analysis assessed the time to the first event, some patients were hospitalized on >1 occasion. The risk of multiple rehospitalizations for any given subject showed a magnitude of event reduction similar to that observed for the time to first event reduction (group 1 versus group 3:

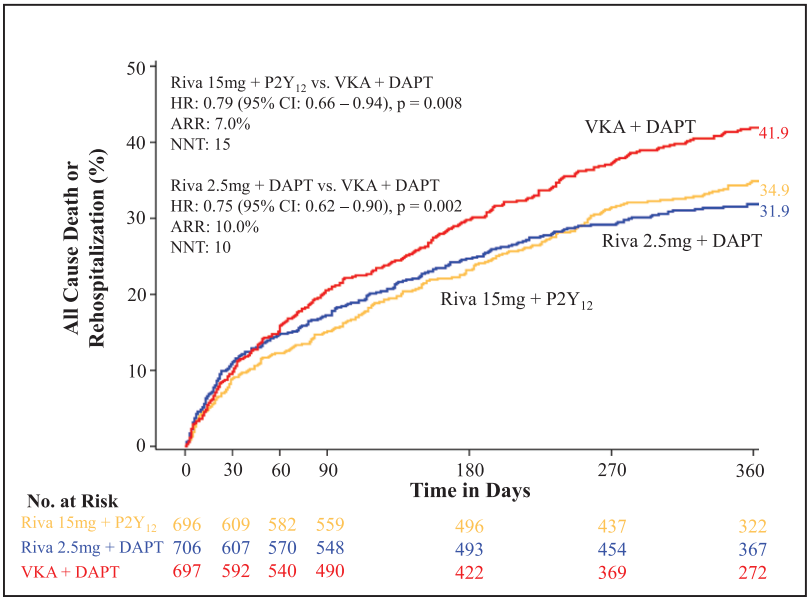

Figure 1. Time to all-cause death or first recurrent hospitalization.
The treatment-emergent period is the period starting after the first study drug administration following randomization and ending 2 days after the study drug was stopped. Hazard ratios (HRs) compared with the vitamin K antagonist (VKA) group are based on the Cox proportional hazards model. Rehospitalizations do not include first index event hospitalization. Log-rank *P* values compared with the VKA group are based on the 2-sided log-rank test. ARR indicates absolute risk reduction; NNT, number needed to treat; Riva+DAPT, rivaroxaban 2.4 mg twice daily plus background dual antiplatelet therapy with low-dose aspirin; and Riva+$P2Y_{12}$, rivaroxaban 15 mg once daily+$P2Y_{12}$ inhibitor.

Table 2. Kaplan-Meier Estimates and HRs for All-Cause Death or First Recurrent Hospitalization

All-Cause Death and Cause of Rehospitalization	Group 1 (n=696)	Group 2 (n=706)	Group 3 (n=697)	Group 1 vs 3, Rivaroxaban+P2Y$_{12}$ vs VKA+DAPT		Group 2 vs 3, Rivaroxaban+DAPT vs VKA+DAPT		Group 1 vs 2, Rivaroxaban+P2Y$_{12}$ vs Rivaroxaban+DAPT	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall	228 (34.89)	213 (31.85)	261 (41.92)	0.79 (0.66–0.94)	0.008	0.75 (0.62–0.90)	0.002	1.06 (0.88–1.28)	0.534
Bleeding or cardiovascular	166 (25.61)	168 (25.26)	225 (36.44)	0.65 (0.54–0.80)	<0.001	0.68 (0.56–0.83)	<0.001	0.97 (0.78–1.20)	0.784
Bleeding	55 (8.62)	51 (7.95)	75 (12.44)	0.69 (0.48–0.97)	0.032	0.64 (0.45–0.91)	0.012	1.07 (0.73–1.56)	0.723
Cardiovascular	136 (21.38)	143 (21.66)	175 (29.26)	0.70 (0.56–0.87)	0.001	0.75 (0.60–0.94)	0.011	0.94 (0.74–1.18)	0.573
Other	106 (16.92)	85 (13.35)	91 (15.48)	1.11 (0.84–1.47)	0.476	0.86 (0.64–1.16)	0.327	1.29 (0.97–1.71)	0.084
All-cause death	16 (2.54)	17 (2.68)	13 (2.25)	1.16 (0.56–2.41)	0.689	1.22 (0.59–2.51)	0.589	0.95 (0.48–1.89)	0.893
DAPT 1 mo, n		108	113						
Overall		48 (45.13)	53 (51.21)			0.92 (0.62–1.35)	0.667		
Bleeding or cardiovascular		36 (33.87)	44 (42.56)			0.80 (0.52–1.24)	0.316		
Bleeding		10 (9.92)	15 (14.70)			0.73 (0.34–1.59)	0.428		
Cardiovascular		31 (29.48)	33 (34.04)			0.91 (0.56–1.48)	0.704		
Other		18 (18.33)	22 (23.41)			0.80 (0.43–1.49)	0.476		
All-cause death		3 (3.00)	2 (2.19)			1.45 (0.24–8.70)	0.681		
DAPT 6 mo, n		248	243						
Overall		80 (34.80)	92 (42.72)			0.84 (0.62–1.13)	0.243		
Bleeding or cardiovascular		60 (26.58)	82 (38.64)			0.68 (0.49–0.95)	0.024		
Bleeding		17 (7.91)	30 (14.25)			0.53 (0.29–0.96)	0.033		
Cardiovascular		52 (23.11)	63 (30.77)			0.80 (0.55–1.15)	0.223		
Other		35 (15.84)	30 (14.68)			1.14 (0.70–1.86)	0.596		
All-cause death		6 (2.75)	6 (3.05)			0.96 (0.31–2.98)	0.944		
DAPT 12 mo, n		350	341						
Overall		85 (25.57)	116 (38.15)			0.63 (0.47–0.83)	0.001		
Bleeding or cardiovascular		72 (21.62)	99 (32.80)			0.64 (0.47–0.86)	0.003		
Bleeding		24 (7.37)	30 (10.42)			0.72 (0.42–1.22)	0.218		
Cardiovascular		60 (18.19)	79 (26.58)			0.67 (0.48–0.93)	0.017		
Other		32 (10.12)	39 (13.44)			0.72 (0.45–1.14)	0.157		
All-cause death		8 (2.52)	5 (1.70)			1.44 (0.47–4.41)	0.518		

CI indicates confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; and VKA, vitamin K antagonist. The treatment-emergent period is the period starting after the first study drug administration after randomization and ending 2 days after cessation of the study drug. The

Kaplan-Meier estimate represents the rate of all-cause death or first rehospitalization from treatment start date to 360 days of study duration.

A subject could have >1 component event. HRs compared with the VKA group (group 1 vs 3 and group 2 vs 3) and rivaroxaban+DAPT (group 1 vs 2) are based on the Cox proportional hazards model.

Rehospitalizations do not include the first index event hospitalization. Log-rank *P* values compared with VKA group are based on the two-sided log rank test.

Numbers are based on the safety population, which includes subjects who received at least 1 dose of the study drug.

HR=0.78, 95% CI, 0.64–0.96 *P*=0.005; group 2 versus group 3: HR=0.75, 95% CI, 0.61–0.92, *P*=0.001; Table 4). There was a highly significant reduction in bleeding or cardiovascular end points combined, but rehospitalization for other causes were not reduced (Table 3 and Figure 4). All adverse events resulting in hospitalization were classified as severe, moderate, or mild. Significant reductions were seen in moderate adverse events, the most common classification, for both rivaroxaban arms. Adverse events categorized as severe bleeding events were reduced in the 15 mg rivaroxaban plus P2Y$_{12}$ monotherapy arm (*P*=0.021) and the 2.5 mg rivaroxaban plus DAPT arm (*P*=0.003), and trends favoring the rivaroxaban arms were seen for a reduction in severe and mild events in general (Table III in the online-only Data Supplement).

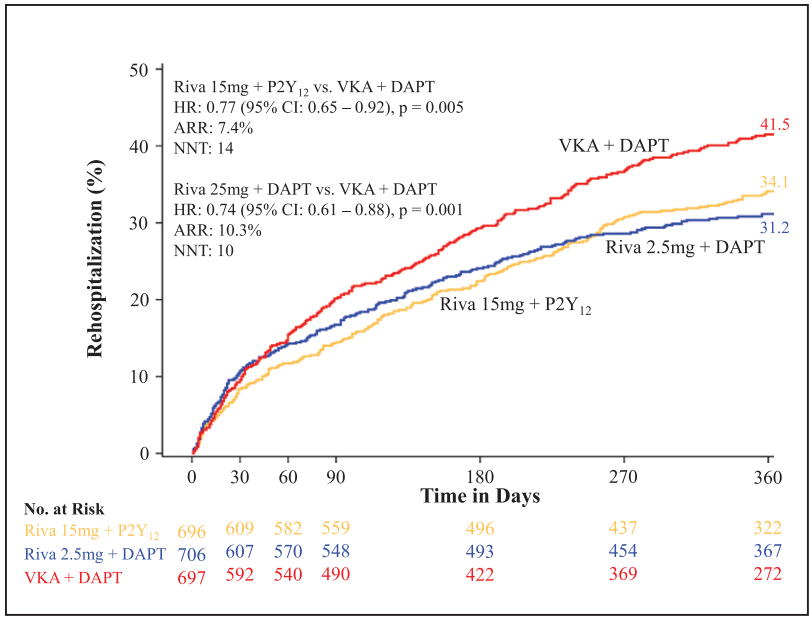

Figure 2. Time to first recurrent hospitalization.
The treatment-emergent period is the period starting after the first study drug administration following randomization and ending 2 days after the study drug was stopped. Hazard ratios (HRs) compared with the vitamin K antagonist (VKA) group are based on the Cox proportional hazards model. Rehospitalizations do not include first index event hospitalization. Log-rank *P* values compared with VKA group are based on the 2-sided log-rank test. ARR indicates absolute risk reduction; NNT, number needed to treat; Riva+DAPT, rivaroxaban 2.4 mg twice daily plus background dual antiplatelet therapy with low-dose aspirin; and Riva+P2Y$_{12}$, rivaroxaban 15 mg once daily+P2Y$_{12}$ inhibitor.

DISCUSSION

Among patients with AF undergoing coronary stent placement, the administration of rivaroxaban in either of 2 dose strategies was associated with a reduced risk of all-cause mortality or recurrent hospitalization for any adverse event compared with a VKA plus DAPT. There was a reduction in the risk of both a first rehospitalization and all (any) rehospitalizations for adverse events. The absolute reduction in cardiovascular events was greater but the relative reduction was greater for bleeding in the rivaroxaban arms. The number needed to treat with rivaroxaban to prevent 1 death or hospitalization ranged from 10 for 2.5 mg rivaroxaban+DAPT to 15 for 15 mg rivaroxaban+P2Y$_{12}$ inhibitor. The results of the present analysis add to and strengthen the primary results of the study and demonstrate that the reduction in bleeding and efficacy events was clinically meaningful insofar as it often resulted in fewer hospitalizations in these patients. Although the results of this analysis demonstrate a statistically significant improvement in clinical events, there is also the potential to improve healthcare value because rehospitalization may be costly.

Both the present analysis and the primary report[8] of the primary safety end point (TIMI major+TIMI minor+bleeding requiring medical attention) demonstrated a reduction in bleeding events. In contrast to the results presented here, however, there was no difference in the prespecified occurrence of the rigorously adjudicated composite secondary end point of death, myocardial infarction, and stroke.[8] Recurrent hospitalization is a more frequent end point and is ascertained with greater sensitivity but less specificity than the traditional adjudicated end point of death/myocardial infarction and stroke. As a result, the present analysis had much greater statistical power (90%) to ascertain a 20% difference in the treatment strategies (the magnitude observed in the present analysis), whereas the end points of cardiovascular death/myocardial infarction and stroke had only 16.8% power to ascertain a 20% treatment difference (Table IV in the online-only Data Supplement). Although many hospitalizations did not qualify as a death/myocardial infarction or stroke, underlying thrombosis or ischemia still may have played a role in the hospitalization. The fact that bleeding and cardiovascular events differed among the strategies but other causes of hospitalization did not supports the acceptable specificity of rehospitalization as an end point.

Although adjudication of events in clinical trials is often based on rigorous definitions and meticulously collected source documents, it still relies on an adjudication process, which, although conducted by experts, may still be somewhat subjective. Prior studies have demonstrated that conclusions related to the adjudication of clinical end points often vary across adjudicators, clinical sites, and core laboratories dedicated to an end point, for instance.[11] The rate of concordance varies significantly according to the experience and judgment of the adjudicator, the availability and quality of source documents, and the type of the end point itself.[11] Advantages of using all-cause mortality or rehospitalization as end points are the near certainty of the occurrence and robust documentation of the events (eg, death certificate or insurance claims data or trial data documenting hospital admission), making them objective end points that do not require an adjudicator's interpretation. As a result of these potential advantages, these end points have been referred to as the gold standard of clinical events.[12] In contrast, identification of cause-specific mortality or nonfatal events such as myocardial infarction or

Table 3. Kaplan-Meier Estimates and HRs for First Recurrent Hospitalization

Cause of Rehospitalization	Group 1 (n= 696)	Group 2 (n=706)	Group 3 (n=697)	Group 1 vs. Group 3, Rivaroxaban+P2Y$_{12}$ vs VKA+DAPT		Group 2 vs. Group 3, Rivaroxaban+DAPT vs VKA+DAPT		Group 1 vs. Group 2, Rivaroxaban+P2Y$_{12}$ vs Rivaroxaban+DAPT	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall	221 (34.09)	207 (31.15)	257 (41.51)	0.77 (0.65–0.92)	0.005	0.74 (0.61–0.88)	0.001	1.06 (0.88–1.28)	0.561
Bleeding or cardiovascular	159 (24.73)	158 (23.98)	219 (35.69)	0.64 (0.52–0.79)	<0.001	0.66 (0.54–0.81)	<0.001	0.99 (0.79–1.23)	0.910
Bleeding	41 (6.54)	34 (5.38)	63 (10.54)	0.61 (0.41–0.90)	0.012	0.51 (0.34–0.77)	0.001	1.19 (0.76–1.86)	0.459
Cardiovascular	128 (20.32)	133 (20.34)	169 (28.44)	0.68 (0.54–0.85)	<0.001	0.73 (0.58–0.91)	0.005	0.95 (0.74–1.20)	0.647
Other	91 (14.76)	74 (11.74)	83 (14.31)	1.04 (0.77–1.40)	0.789	0.82 (0.60–1.13)	0.220	1.27 (0.93–1.72)	0.128
DAPT 1 mo, n		108	113						
Overall		48 (45.13)	53 (51.21)			0.92 (0.62–1.35)	0.667		
Bleeding or cardiovascular		35 (33.18)	44 (42.56)			0.78 (0.50–1.21)	0.263		
Bleeding		7 (7.07)	14 (13.76)			0.57 (0.24–1.37)	0.202		
Cardiovascular		30 (28.75)	33 (34.04)			0.88 (0.54–1.44)	0.612		
Other		16 (16.44)	21 (22.55)			0.74 (0.39–1.43)	0.369		
DAPT 6 mo, n		248	243						
Overall		77 (33.81)	90 (42.18)			0.82 (0.61–1.12)	0.209		
Bleeding or cardiovascular		56 (25.13)	79 (37.54)			0.66 (0.47–0.93)	0.017		
Bleeding		11 (5.27)	24 (11.39)			0.43 (0.21–0.87)	0.016		
Cardiovascular		48 (21.60)	60 (29.60)			0.77 (0.53–1.13)	0.182		
Other		32 (14.66)	27 (13.42)			1.16 (0.69–1.93)	0.572		
DAPT 12 mo, n		350	341						
Overall		82 (24.83)	114 (37.69)			0.62 (0.46–0.82)	<0.001		
Bleeding or cardiovascular		67 (20.28)	96 (32.02)			0.61 (0.45–0.83)	0.002		
Bleeding		16 (4.95)	25 (8.87)			0.57 (0.31–1.07)	0.076		
Cardiovascular		55 (16.80)	76 (25.73)			0.64 (0.45–0.90)	0.010		
Other		26 (8.32)	35 (12.23)			0.65 (0.39–1.07)	0.088		

CI indicates confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; and VKA, vitamin K antagonist. The treatment-emergent period is the period starting after the first study drug administration aftr randomization and ending 2 days after cessation of the study drug.

The Kaplan-Meier estimate represents the rate of first rehospitalization from the treatment start date to 360 days of study duration.

A subject could have >1 component event. HRs compared with the VKA group (group 1 vs 3 and group 2 vs 3) and rivaroxaban+DAPT (group 1 vs 2) are based on the Cox proportional hazards model.

Rehospitalizations do not include first index event hospitalization. Log-rank *P* values compared with the VKA group are based on the 2-sided log-rank test.

Numbers are based on the safety population, which includes subjects who received at least 1 dose of the study drug.

stroke may be complex, inconsistent, and often inferred (eg, assuming that all unidentified causes of death are cardiovascular deaths). Although subjects with myocardial infarctions and strokes are hospitalized to establish these diagnoses, deaths may occur without hospitalization, and for this reason, it is critical that all-cause death be added to the end point of hospitalization. In addition, all-cause mortality and rehospitalization are comprehensive end points that encompass the occurrence of both efficacy and safety events. For example, in evaluations of all-cause mortality, death resulting from a myocardial infarction (efficacy end point) carries a similar weight as death resulting from significant gastrointestinal bleeding (safety end point) with no need to distinguish between two. Prior studies such as the ATHENA trial (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation), which supported the approval of dronedarone for treatment of nonpermanent AF, have used the composite of hospitalization and all-cause death as a primary means to evaluate the efficacy and safety of a therapeutic strategy.[13,14]

Hospitalizations may not have been due to a death/myocardial infarction or stroke but may nonetheless be associated with a poor quality of life and higher costs.

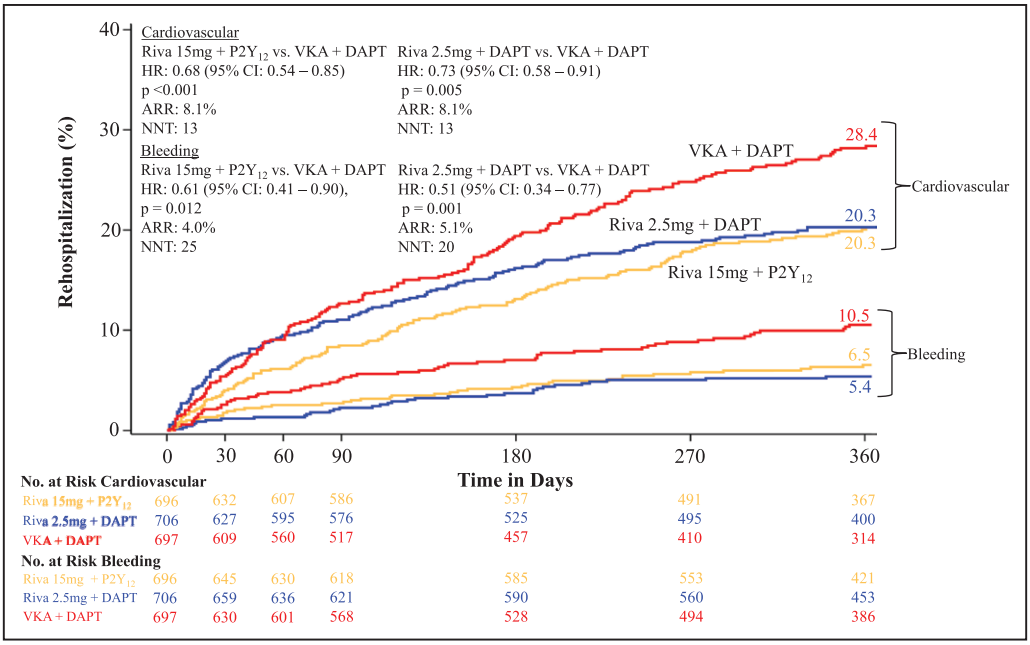

Figure 3. Time to first recurrent hospitalization caused by cardiovascular or bleeding event.
The treatment-emergent period is the period starting after the first study drug administration following randomization and ending 2 days after the study drug was stopped. Hazard ratios (HRs) compared with the vitamin K antagonist (VKA) group are based on the Cox proportional hazards model. Rehospitalizations do not include first index event hospitalization. Log-rank *P* values compared with the VKA group are based on the 2-sided log-rank test. ARR indicates absolute risk reduction; NNT, number needed to treat; Riva+DAPT, rivaroxaban 2.4 mg twice daily plus background dual antiplatelet therapy with low-dose aspirin; and Riva+P2Y$_{12}$, rivaroxaban 15 mg once daily+P2Y$_{12}$ inhibitor.

Because costs for rehospitalizations after percutaneous coronary intervention involving bleeding and cardiovascular events are substantial, a 10% absolute and a 25% relative reduction in the risk of hospitalization would likely be associated with a reduction in healthcare costs. The costs of a bleeding event associated with a VKA is

Table 4. HRs and 95% CIs for Time to Multiple Recurrent Hospitalizations

				Group 1 vs Group 3, Rivaroxaban+P2Y$_{12}$ vs VKA+DAPT		Group 2 vs Group 3, Rivaroxaban+DAPT vs VKA+DAPT		Group 1 vs Group 2, Rivaroxaban+P2Y$_{12}$ vs Rivaroxaban+DAPT	
	Group 1 (n=696)	Group 2 (n=706)	Group 3 (n=697)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall, n (%)	325 (46.70)	311 (44.05)	377 (54.09)	0.78 (0.64–0.96)	0.005	0.75 (0.61–0.92)	0.001	1.05 (0.84–1.31)	0.562
DAPT 1 mo, n		108	113						
n (%)		75 (69.44)	81 (71.68)			0.91 (0.58–1.42)	0.647		
DAPT 6 mo, n		248	243						
n (%)		123 (49.60)	129 (53.09)			0.91 (0.63–1.30)	0.234		
DAPT 12 mo, n		350	341						
n (%)		113 (32.29)	167 (48.97)			0.58 (0.43–0.79)	<0.001		

CI indicates confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; and VKA, vitamin K antagonist. The HR is calculated with the Wei-Lin-Weissfeld method for multiple events. The overall HR presented here is the average across all rehospitalization events, not including the index hospitalization event. The treatment-emergent period is the period starting after the first study drug administration after randomization and ending 2 days after cessation of the study drug.

Numbers are based on the safety population, which includes subjects who received at least 1 dose of study drug.

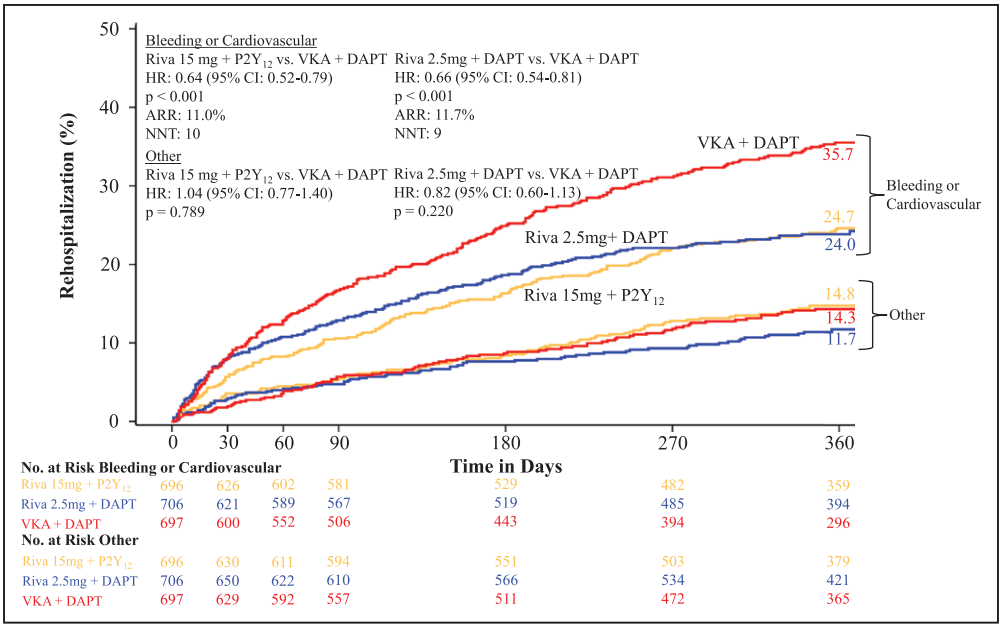

Figure 4. Time to first recurrent hospitalization caused by combined bleeding or cardiovascular event or other event. The treatment-emergent period is the period starting after the first study drug administration following randomization and ending 2 days after the study drug was stopped. Hazard ratios (HRs) compared with the vitamin K antagonist (VKA) group are based on the Cox proportional hazards model. Rehospitalizations do not include first index event hospitalization. Log-rank *P* values compared with the VKA group are based on the 2-sided log-rank test. ARR indicates absolute risk reduction; NNT, number needed to treat; Riva+DAPT, rivaroxaban 2.4 mg twice daily plus background dual antiplatelet therapy with low-dose aspirin; and Riva+P2Y$_{12}$, rivaroxaban 15 mg once daily+P2Y$_{12}$ inhibitor.

estimated to be approximately US $8000 (2011 estimate),[15,16] similar to costs for common cardiovascular conditions such as chest pain (≈$8000), heart failure (≈$10 000), and percutaneous coronary intervention (≈$25 000) that result in rehospitalization. In addition, the total cost of international normalized ratio monitoring per year has been estimated to be $2134 in the first year and $1170 per year thereafter as long as stable levels have been attained.[17]

The results of the study stratified by DAPT duration are of interest to practicing clinicians. However, there are limitations to exploring the results in these subgroups. There was a negative interaction term for DAPT duration for the end point of all-cause mortality and rehospitalization, and the validity of interrogating these subgroups is questionable. The decision to treat patients with 1, 6, or 12 months of DAPT was not randomized and was based on clinician preference. As might be expected, there were imbalances in patient characteristics across the DAPT duration strata (Table V in the online-only Data Supplement) and imbalances in patient characteristics within each DAPT duration stratum across the 3 treatment strategies (Tables VI–VIII in the online-only Data Supplement). In addition to imbalances in these identified confounders, there are likely imbalances in unidentified confounders. Last, there was no adjustment for multiplicity in testing for these subgroups and others.

The results presented here are generally applicable to those patients treated with clopidogrel. Given the small number of patients treated with novel thienopyridines, additional trials would be required to more rigorously assess both the safety and efficacy of concomitant therapy with prasugrel or ticagrelor in a larger population.

Limitations

The present analysis is a post hoc analysis. No adjustment was made to account for multiple testing. Accordingly, statistically significant differences between the groups should be interpreted in this context. The method of allocating events to bleeding, cardiovascular, or other causes was not described a priori. This methodology could be prospectively applied by others using the extensive tables provided in the online-only Data Supplement that describe how these adverse events can be mapped into the 3 categories. This analysis is based on a randomized, controlled trial with specific inclusion and exclusion criteria (including the exclusion of patients at high risk of bleeding), and the results of the study may not be generalizable to all patients in clinical practice. Hospital bills and length of stay were not collected to assess costs. Although the 2.5 mg twice daily plus DAPT dosing regimen is currently indicated and available in Europe and a number of other countries for the secondary prevention of acute coronary syndrome events, the

15/10 mg once daily dosing strategy studied here is currently not approved for the management of patients with either acute coronary syndrome or AF. Sites were unblinded with respect to warfarin therapy, although clinical event categorization was blinded. It could be argued that there was a general bias to admit more patients on open-label VKA to the hospital. The increase in rehospitalization, however, was attributable exclusively to bleeding and cardiovascular causes alone. There was no difference among the 3 strategies with respect to rehospitalization for all other types of adverse events, indicating that clinicians were not biased in attributing all types of additional hospitalizations in general to VKA+DAPT.

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FOOTNOTES

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Recurrent Hospitalization Among Patients With Atrial Fibrillation Undergoing Intracoronary Stenting Treated With 2 Treatment Strategies of Rivaroxaban or a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy

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SUPPLEMENTAL MATERIAL

Table S1. Line Listing of all adverse events requiring hospitalization and their categorization as either bleeding, cardiovascular or other

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Abdominal Pain	Other	4	0.4
Abdominal Pain Lower	Other	1	0.1
Abdominal Wall Abscess	Other	2	0.2
Abscess Limb	Other	1	0.1
Acute Abdomen	Other	1	0.1
Acute Coronary Syndrome	Cardiovascular	4	0.4
Acute Kidney Injury	Other	5	0.5
Acute Myocardial Infarction	Cardiovascular	12	1.1
Acute Pulmonary Oedema	Cardiovascular	3	0.3
Acute Respiratory Failure	Cardiovascular	2	0.2
Adrenal Neoplasm	Other	1	0.1
Age-Related Macular Degeneration	Other	1	0.1
Ameloblastoma	Other	1	0.1
Anaemia	Bleeding	10	0.9
Anal Fistula	Other	1	0.1
Anal Haemorrhage	Bleeding	2	0.2
Anaphylactic Shock	Other	1	0.1
Angina Pectoris	Cardiovascular	40	3.7
Angina Unstable	Cardiovascular	53	4.9
Angioplasty	Cardiovascular	1	0.1
Anxiety	Other	1	0.1
Anxiety Disorder	Other	1	0.1
Aortic Aneurysm	Cardiovascular	1	0.1
Aortic Stenosis	Cardiovascular	3	0.3
Aortic Valve Replacement	Cardiovascular	1	0.1
Aphasia	Cardiovascular	1	0.1
Appendicitis	Other	2	0.2
Arterial Stenosis	Cardiovascular	2	0.2
Arteriosclerosis	Cardiovascular	1	0.1
Arteriovenous Fistula	Cardiovascular	1	0.1
Arthralgia	Other	3	0.3
Arthritis	Other	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Arthritis Bacterial	Other	2	0.2
Atrial Fibrillation	Cardiovascular	70	6.5
Atrial Flutter	Cardiovascular	9	0.8
Atrial Tachycardia	Cardiovascular	4	0.4
Atrial Thrombosis	Cardiovascular	3	0.3
Atrioventricular Block	Cardiovascular	3	0.3
Atrioventricular Block Complete	Cardiovascular	1	0.1
Back Pain	Other	2	0.2
Bacterial Sepsis	Other	1	0.1
Barrett's Oesophagus	Other	1	0.1
Basal Cell Carcinoma	Other	1	0.1
Bile Duct Stone	Other	1	0.1
Biopsy Prostate	Other	1	0.1
Bladder Cancer	Other	1	0.1
Bladder Neoplasm	Other	1	0.1
Bladder Tamponade	Bleeding	1	0.1
Bowen's Disease	Other	2	0.2
Bradyarrhythmia	Cardiovascular	1	0.1
Bradycardia	Cardiovascular	5	0.5
Brain Neoplasm Malignant	Other	1	0.1
Bronchial Carcinoma	Other	1	0.1
Bronchitis	Other	5	0.5
Bronchitis Bacterial	Other	1	0.1
Bronchopneumopathy	Other	1	0.1
Bursitis	Other	1	0.1
Calculus Ureteric	Other	1	0.1
Calculus Urethral	Other	1	0.1
Calculus Urinary	Other	1	0.1
Cardiac Ablation	Cardiovascular	2	0.2
Cardiac Arrest	Cardiovascular	1	0.1
Cardiac Disorder	Cardiovascular	1	0.1
Cardiac Failure	Cardiovascular	74	6.9
Cardiac Failure Acute	Cardiovascular	8	0.7
Cardiac Failure Chronic	Cardiovascular	8	0.7
Cardiac Failure Congestive	Cardiovascular	25	2.3
Cardiac Pacemaker Insertion	Cardiovascular	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Cardiac Pseudoaneurysm	Cardiovascular	1	0.1
Cardiac Resynchronisation Therapy	Cardiovascular	1	0.1
Cardiac Stress Test	Cardiovascular	1	0.1
Cardiogenic Shock	Cardiovascular	2	0.2
Cardiomyopathy	Cardiovascular	2	0.2
Cardiovascular Disorder	Cardiovascular	1	0.1
Cardioversion	Cardiovascular	2	0.2
Carotid Artery Stenosis	Cardiovascular	1	0.1
Cataract	Other	4	0.4
Catheter Site Swelling	Cardiovascular	1	0.1
Cellulitis	Other	4	0.4
Cerebral Haemorrhage	Bleeding	8	0.7
Cerebral Infarction	Cardiovascular	1	0.1
Cerebral Ischaemia	Cardiovascular	1	0.1
Cerebrovascular Accident	Cardiovascular	3	0.3
Cervical Polyp	Other	1	0.1
Change Of Bowel Habit	Other	1	0.1
Chest Discomfort	Cardiovascular	1	0.1
Chest Pain	Cardiovascular	22	2.0
Cholangiocarcinoma	Other	1	0.1
Cholangitis	Other	1	0.1
Cholecystectomy	Other	2	0.2
Cholecystitis	Other	3	0.3
Cholecystitis Acute	Other	3	0.3
Cholecystitis Chronic	Other	1	0.1
Cholelithiasis	Other	4	0.4
Chronic Obstructive Pulmonary Disease	Other	8	0.7
Circulatory Collapse	Cardiovascular	1	0.1
Clostridium Difficile Colitis	Other	1	0.1
Colon Cancer	Other	1	0.1
Colorectal Adenocarcinoma	Other	1	0.1
Compression Fracture	Other	1	0.1
Concussion	Bleeding	1	0.1
Confusional State	Cardiovascular	1	0.1
Constipation	Other	3	0.3
Contusion	Bleeding	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Coronary Arterial Stent Insertion	Cardiovascular	1	0.1
Coronary Artery Bypass	Cardiovascular	1	0.1
Coronary Artery Disease	Cardiovascular	11	1.0
Coronary Artery Stenosis	Cardiovascular	2	0.2
Coronary Artery Thrombosis	Cardiovascular	1	0.1
Craniocerebral Injury	Cardiovascular	1	0.1
Crohn's Disease	Other	1	0.1
Cystitis	Other	1	0.1
Deafness Neurosensory	Other	1	0.1
Deep Vein Thrombosis	Cardiovascular	1	0.1
Dehydration	Other	2	0.2
Delirium	Cardiovascular	1	0.1
Depression	Other	1	0.1
Device Failure	Cardiovascular	1	0.1
Diabetes Mellitus	Other	3	0.3
Diabetic Foot	Other	1	0.1
Diabetic Metabolic Decompensation	Other	1	0.1
Diarrhoea	Other	2	0.2
Diffuse Large B-Cell Lymphoma	Other	1	0.1
Diverticulitis	Other	1	0.1
Dizziness	Cardiovascular	2	0.2
Dizziness Postural	Cardiovascular	1	0.1
Drug Intolerance	Other	1	0.1
Drug Withdrawal Syndrome	Other	1	0.1
Dysphagia	Other	1	0.1
Dyspnoea	Cardiovascular	27	2.5
Dyspnoea At Rest	Cardiovascular	1	0.1
Dyspnoea Exertional	Cardiovascular	4	0.4
Ejection Fraction Decreased	Cardiovascular	1	0.1
Electrocardiogram Ambulatory Abnormal	Cardiovascular	1	0.1
Encephalitis Viral	Other	1	0.1
Encephalopathy	Other	1	0.1
Enteritis	Other	1	0.1
Enterocolitis	Other	1	0.1
Epididymitis	Other	1	0.1
Epilepsy	Other	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Epistaxis	Bleeding	16	1.5
Erysipelas	Other	1	0.1
Exostosis	Other	1	0.1
Extremity Necrosis	Cardiovascular	1	0.1
Eye Haemorrhage	Bleeding	1	0.1
Faecaloma	Other	1	0.1
Fall	Other	4	0.4
Fatigue	Cardiovascular	1	0.1
Femoral Artery Occlusion	Cardiovascular	2	0.2
Femoral Neck Fracture	Other	2	0.2
Gait Disturbance	Cardiovascular	1	0.1
Gangrene	Cardiovascular	3	0.3
Gastric Haemorrhage	Bleeding	1	0.1
Gastric Mucosa Erythema	Other	1	0.1
Gastric Ulcer	Bleeding	6	0.6
Gastric Ulcer Haemorrhage	Bleeding	1	0.1
Gastritis	Other	4	0.4
Gastritis Erosive	Bleeding	4	0.4
Gastritis Haemorrhagic	Bleeding	3	0.3
Gastroduodenitis Haemorrhagic	Bleeding	1	0.1
Gastroenteritis	Other	4	0.4
Gastrointestinal Haemorrhage	Bleeding	21	2.0
Gastrointestinal Infection	Other	1	0.1
Gastrointestinal Stromal Tumour	Other	1	0.1
Gastrointestinal Ulcer	Bleeding	1	0.1
Gastrooesophageal Reflux Disease	Other	2	0.2
Gouty Arthritis	Other	2	0.2
Haemarthrosis	Bleeding	1	0.1
Haematochezia	Bleeding	2	0.2
Haematoma	Bleeding	3	0.3
Haematoma Infection	Bleeding	1	0.1
Haematuria	Bleeding	11	1.0
Haemoglobin Decreased	Bleeding	1	0.1
Haemoptysis	Bleeding	8	0.7
Haemorrhage	Bleeding	2	0.2
Haemorrhage Urinary Tract	Bleeding	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Haemorrhagic Anaemia	Bleeding	1	0.1
Haemorrhagic Stroke	Bleeding	2	0.2
Haemorrhoidal Haemorrhage	Bleeding	1	0.1
Haemorrhoids	Other	1	0.1
Haemothorax	Bleeding	1	0.1
Hallucination	Other	1	0.1
Hemiparesis	Cardiovascular	1	0.1
Hepatic Cyst	Other	1	0.1
Hepatitis Acute	Other	1	0.1
Hepatocellular Carcinoma	Other	1	0.1
Herpes Zoster	Other	1	0.1
Hiatus Hernia	Other	1	0.1
Hip Fracture	Other	1	0.1
Hospitalisation	Other	1	0.1
Humerus Fracture	Other	2	0.2
Hydronephrosis	Other	2	0.2
Hypergammaglobulinaemia	Other	1	0.1
Hyperglycaemia	Other	2	0.2
Hypertension	Cardiovascular	7	0.7
Hypertensive Crisis	Cardiovascular	7	0.7
Hyperthyroidism	Other	1	0.1
Hypoaesthesia	Other	1	0.1
Hypochromic Anaemia	Bleeding	1	0.1
Hypokalaemia	Other	1	0.1
Hyponatraemia	Cardiovascular	1	0.1
Hypotension	Cardiovascular	1	0.1
Ileostomy Closure	Other	1	0.1
Impaired Gastric Emptying	Other	1	0.1
Implantable Defibrillator Insertion	Cardiovascular	4	0.4
Incisional Hernia	Other	1	0.1
Infected Skin Ulcer	Other	1	0.1
Infective Exacerbation Of Chronic Obstructive Airways Disease	Other	3	0.3
Influenza	Other	2	0.2
Inguinal Hernia	Other	4	0.4
Intercostal Neuralgia	Other	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Intermittent Claudication	Cardiovascular	3	0.3
International Normalised Ratio Increased	Cardiovascular	3	0.3
Interstitial Lung Disease	Other	1	0.1
Intervertebral Disc Protrusion	Other	1	0.1
Intestinal Ischaemia	Cardiovascular	2	0.2
Intestinal Obstruction	Other	1	0.1
Intra-Abdominal Haematoma	Bleeding	1	0.1
Intracranial Haematoma	Bleeding	1	0.1
Ischaemic Cardiomyopathy	Cardiovascular	1	0.1
Ischaemic Stroke	Cardiovascular	9	0.8
Jaundice	Other	1	0.1
Joint Effusion	Other	1	0.1
Knee Arthroplasty	Other	3	0.3
Lacunar Infarction	Cardiovascular	2	0.2
Left Ventricular Dysfunction	Cardiovascular	2	0.2
Left Ventricular Failure	Cardiovascular	2	0.2
Liver Abscess	Other	1	0.1
Localised Infection	Other	1	0.1
Lower Gastrointestinal Haemorrhage	Bleeding	2	0.2
Lower Limb Fracture	Other	1	0.1
Lower Respiratory Tract Infection	Other	1	0.1
Lumbar Spinal Stenosis	Other	1	0.1
Lung Neoplasm Malignant	Other	2	0.2
Lymphocele	Other	1	0.1
Malaise	Cardiovascular	1	0.1
Malignant Hypertension	Cardiovascular	2	0.2
Mallory-Weiss Syndrome	Bleeding	1	0.1
Medical Device Complication	Cardiovascular	1	0.1
Melaena	Bleeding	6	0.6
Meningioma	Other	1	0.1
Metabolic Disorder	Other	1	0.1
Microcytic Anaemia	Bleeding	2	0.2
Mitral Valve Repair	Cardiovascular	1	0.1
Mouth Haemorrhage	Bleeding	1	0.1
Multi-Organ Failure	Cardiovascular	1	0.1
Muscle Rupture	Other	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Musculoskeletal Disorder	Other	1	0.1
Myocardial Infarction	Cardiovascular	2	0.2
Myocardial Ischaemia	Cardiovascular	3	0.3
Nasopharyngitis	Other	1	0.1
Nausea	Other	1	0.1
Neck Pain	Other	1	0.1
Neoplasm	Other	1	0.1
Neuralgia	Other	1	0.1
Neurodermatitis	Other	1	0.1
Non-Cardiac Chest Pain	Cardiovascular	4	0.4
Oedema Peripheral	Cardiovascular	2	0.2
Osteoarthritis	Other	5	0.5
Osteochondrosis	Other	1	0.1
Overdose	Other	5	0.5
Pain In Extremity	Other	2	0.2
Palpitations	Cardiovascular	3	0.3
Pancreatitis	Other	3	0.3
Pancreatitis Chronic	Other	1	0.1
Parkinson's Disease	Other	1	0.1
Percutaneous Coronary Intervention	Cardiovascular	1	0.1
Periarthritis	Other	1	0.1
Pericardial Effusion	Cardiovascular	1	0.1
Pericardial Haemorrhage	Bleeding	1	0.1
Pericarditis	Cardiovascular	1	0.1
Periodontitis	Other	1	0.1
Peripheral Arterial Occlusive Disease	Cardiovascular	6	0.6
Peripheral Artery Thrombosis	Cardiovascular	3	0.3
Peripheral Embolism	Cardiovascular	1	0.1
Peripheral Ischaemia	Cardiovascular	4	0.4
Peripheral Vascular Disorder	Cardiovascular	1	0.1
Pituitary Tumour Benign	Other	1	0.1
Pleural Effusion	Cardiovascular	1	0.1
Pneumonia	Other	37	3.4
Pneumothorax Traumatic	Other	1	0.1
Post Procedural Haematoma	Bleeding	1	0.1
Post Procedural Haemorrhage	Bleeding	2	0.2

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Presyncope	Cardiovascular	1	0.1
Prostate Cancer	Other	2	0.2
Pubis Fracture	Other	1	0.1
Pulmonary Congestion	Cardiovascular	1	0.1
Pulmonary Hypertension	Cardiovascular	4	0.4
Pulmonary Mass	Other	1	0.1
Pulmonary Oedema	Cardiovascular	5	0.5
Pyelonephritis	Other	1	0.1
Pyrexia	Other	1	0.1
Radius Fracture	Other	1	0.1
Rectal Cancer	Other	2	0.2
Rectal Haemorrhage	Bleeding	8	0.7
Rectal Neoplasm	Other	1	0.1
Renal Artery Stenosis	Cardiovascular	1	0.1
Renal Cell Carcinoma	Other	1	0.1
Renal Failure	Other	2	0.2
Renal Impairment	Other	1	0.1
Renal Neoplasm	Other	1	0.1
Renal Sympathetic Nerve Ablation	Other	1	0.1
Respiratory Distress	Cardiovascular	1	0.1
Respiratory Failure	Cardiovascular	1	0.1
Respiratory Tract Infection	Other	2	0.2
Rhabdomyolysis	Other	1	0.1
Rheumatic Disorder	Other	1	0.1
Rib Fracture	Other	2	0.2
Road Traffic Accident	Other	1	0.1
Sciatica	Other	1	0.1
Scrotal Abscess	Other	1	0.1
Sepsis	Other	3	0.3
Septic Shock	Other	2	0.2
Sinus Bradycardia	Cardiovascular	1	0.1
Sinus Node Dysfunction	Cardiovascular	8	0.7
Skin Necrosis	Cardiovascular	2	0.2
Skin Ulcer	Other	1	0.1
Sleep Apnoea Syndrome	Other	3	0.3
Small Cell Lung Cancer Metastatic	Other	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Small Intestinal Obstruction	Other	1	0.1
Spinal Column Stenosis	Other	1	0.1
Spinal Disorder	Other	1	0.1
Spinal Osteoarthritis	Other	1	0.1
Spinal Pain	Other	1	0.1
Squamous Cell Carcinoma	Other	1	0.1
Stomatitis	Other	1	0.1
Subdural Haematoma	Bleeding	2	0.2
Subdural Haemorrhage	Bleeding	2	0.2
Supraventricular Tachycardia	Cardiovascular	3	0.3
Syncope	Cardiovascular	15	1.4
Tachyarrhythmia	Cardiovascular	1	0.1
Tachycardia Induced Cardiomyopathy	Cardiovascular	1	0.1
Tension Headache	Other	1	0.1
Tongue Haemorrhage	Bleeding	1	0.1
Tooth Extraction	Other	1	0.1
Tracheitis	Other	1	0.1
Transient Ischaemic Attack	Cardiovascular	5	0.5
Traumatic Fracture	Other	2	0.2
Traumatic Haematoma	Bleeding	1	0.1
Tuberculosis	Other	1	0.1
Ulcer Haemorrhage	Bleeding	1	0.1
Upper Gastrointestinal Haemorrhage	Bleeding	4	0.4
Upper Limb Fracture	Other	1	0.1
Upper Respiratory Tract Infection	Other	1	0.1
Urethral Haemorrhage	Bleeding	1	0.1
Urethral Stenosis	Other	1	0.1
Urinary Retention	Other	2	0.2
Urinary Tract Infection	Other	6	0.6
Urosepsis	Other	1	0.1
Urticaria	Other	1	0.1
Vascular Pseudoaneurysm	Cardiovascular	2	0.2
Vascular Stent Occlusion	Cardiovascular	1	0.1
Vascular Stent Restenosis	Cardiovascular	2	0.2
Vascular Stent Thrombosis	Cardiovascular	3	0.3
Venous Thrombosis	Cardiovascular	1	0.1

Adverse event leading to rehospitalization	Category	Frequency Count	Percent of Total Frequency
Ventricular Extrasystoles	Cardiovascular	1	0.1
Ventricular Fibrillation	Cardiovascular	4	0.4
Ventricular Tachycardia	Cardiovascular	3	0.3
Vertigo	Other	1	0.1
Vessel Puncture Site Haematoma	Bleeding	1	0.1
Viral Upper Respiratory Tract Infection	Other	1	0.1
Vitreous Haemorrhage	Bleeding	1	0.1
Wound Dehiscence	Other	1	0.1

Table S2: Baseline Characteristics (Cont.)

Characteristic	Group 1 Rivaroxaban + $P2Y_{12}$ (N=709)	Group 2 Rivaroxaban + DAPT (N=709)	Group 3 VKA + DAPT (N=706)
BMI, median (IQR) †	28.6 (25.7 – 32.4)	28.4 (25.6 – 32.1)	29.0 (25.8 – 32.8)
Urgency of Revascularization – no. (%)			
Elective	428 (60.4)	430 (60.6)	449 (63.6)
Urgent	281 (39.6)	279 (39.4)	257 (36.4)
$CHADS_2$ risk of stroke – no. (%)			
0	99 (14.0)	90 (12.7)	83 (11.8)
1	220 (31.0)	232 (32.7)	227 (32.2)
2	246 (34.7)	256 (36.1)	273 (38.7)
3	128 (18.1)	118 (16.6)	107 (15.2)
4	16 (2.3)	13 (1.8)	16 (2.3)
5	0 (0.0)	0 (0.0)	0 (0.0)
6	0 (0.0)	0 (0.0)	0 (0.0)
HAS Bled Score – no. (%)			
0	2 (0.3)	2 (0.3)	0 (0.0)
1	28 (4.0)	43 (6.1)	26 (3.7)
2	166 (23.4)	182 (25.7)	182 (25.8)
3	321 (45.3)	294 (41.5)	308 (43.6)
4	160 (22.6)	157 (22.1)	157 (22.2)
5	31 (4.4)	30 (4.2)	31 (4.4)
6	1 (0.1)	1 (0.1)	2 (0.3)
Comorbidities – no. (%)			
Congestive heart failure	180 (25.4)	187 (26.4)	175 (24.8)
Hypertension	520 (73.3)	519 (73.2)	532 (75.4)
Diabetes mellitus	204 (28.8)	199 (28.1)	221 (31.3)
Hypercholesterolemia	302 (42.6)	295 (41.6)	316 (44.8)
Previous myocardial infarction	140 (19.8)	180 (25.4)	157 (22.2)
Peripheral vascular disease	30 (4.2)	42 (5.9)	35 (5.0)
Gastrointestinal bleeding	7 (1.0)	9 (1.3)	5 (0.7)
Medications – no. (%)			
Aspirin¥	9 (1.3)	702 (99.7)	699 (99.6)
Beta-blocker	586 (82.7)	541 (76.3)	537 (76.1)
ACE inhibitor or ARB	571 (80.5)	532 (75.0)	537 (76.1)
Statin	596 (84.1)	557 (78.6)	552 (78.2)
Proton pump inhibitor			
Omeprazole or esomeprazole	74 (10.4)	78 (11.0)	79 (11.2)
Other	200 (28.2)	198 (27.9)	180 (25.5)

¥ Aspirin use was calculated as administration of aspirin no more than 4 days after PCI procedure for index event.
There were significant differences across groups in the following categories; previous myocardial infarction (p=0.039 overall, p=0.011 Group 1 v Group 2), aspirin use (p<0.001 overall, p<0.001 Group 1 v Group 2, p<0.001 Group 1 v Group 3), beta-blocker use (p=0.003 overall, p=0.002 Group 1 v Group 3, p=0.003 Group 1 v Group 2), ACE inhibitor or ARB use (p=0.032 overall, p=0.042 Group 1 v Group 3, p=0.013 Group 1 v Group 2) and statin use (p=0.008 overall, p=0.005 Group 1 v Group 3, p=0.008 Group 1 v Group 2). All other p-values were not significant.
Note: Plus-minus values are mean ± SD. There were no significant differences among the three groups. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, BMI denotes body mass index.
Note: Numbers based upon all randomized subjects.
Note: Pairwise comparisons were calculated using the chi-square test of independence for categorical variables, independent samples t-test for parametric continuous variables, and Wilcoxon rank sum test for non-parametric continuous variables.

Table S3: Rate of Events Leading to Recurrent Hospitalization by Severity

Endpoint	Group 1 (N= 696)	Group 2 (N=706)	Group 3 (N=697)	Group 1 vs. Group 3 Rivaroxaban + $P2Y_{12}$ vs. VKA + DAPT		Group 2 vs. Group 3 Rivaroxaban + DAPT vs. VKA + DAPT	
				HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Overall	**221 (34.1)**	**207 (31.2)**	**257 (41.5)**	**0.77 (0.65 – 0.92)**	**0.005**	**0.74 (0.61 – 0.88)**	**0.001**
Severe	70 (11.1)	74 (11.4)	83 (13.8)	0.78 (0.57 – 1.08)	0.13	0.84 (0.62 – 1.15)	0.28
Moderate	142 (22.7)	120 (18.7)	163 (27.3)	0.80 (0.64 – 1.00)	0.05	0.68 (0.54 – 0.86)	0.001
Mild	53 (8.6)	54 (8.5)	56 (9.8)	0.88 (0.61 – 1.28)	0.51	0.90 (0.62 – 1.30)	0.56
Bleeding or Cardiovascular	**159 (24.7)**	**158 (24.0)**	**219 (35.7)**	**0.64 (0.52 – 0.79)**	**<0.001**	**0.66 (0.54 – 0.81)**	**<0.001**
Severe	51 (8.2)	56 (8.6)	64 (10.6)	0.74 (0.51 – 1.07)	0.11	0.84 (0.59 – 1.20)	0.33
Moderate	99 (15.9)	84 (13.1)	135 (22.7)	0.67 (0.52 – 0.87)	0.002	0.57 (0.44 – 0.75)	<0.001
Mild	30 (4.8)	43 (6.8)	46 (8.0)	0.61 (0.38 – 0.96)	0.031	0.87 (0.57 – 1.32)	0.51
Bleeding	**41 (6.5)**	**34 (5.4)**	**63 (10.5)**	**0.61 (0.41 – 0.90)**	**0.012**	**0.51 (0.34 – 0.77)**	**0.001**
Severe	12 (1.9)	8 (1.3)	25 (4.2)	0.45 (0.23 – 0.90)	0.021	0.34 (0.16 – 0.72)	0.003
Moderate	23 (3.7)	20 (3.2)	33 (5.7)	0.65 (0.38 – 1.11)	0.12	0.56 (0.32 – 0.97)	0.037
Mild	6 (1.0)	7 (1.1)	6 (1.0)	0.95 (0.31 – 2.93)	0.92	1.09 (0.37 – 3.24)	0.88
Cardiovascular	**128 (20.3)**	**133 (20.3)**	**169 (28.4)**	**0.68 (0.54 – 0.85)**	**<0.001**	**0.73 (0.58 – 0.91)**	**0.005**
Severe	39 (6.3)	48 (7.4)	41 (6.9)	0.89 (0.57 – 1.38)	0.59	1.10 (0.73 – 1.67)	0.64
Moderate	80 (12.9)	66 (10.3)	107 (18.3)	0.68 (0.51 – 0.91)	0.009	0.57 (0.42 – 0.78)	<0.001
Mild	26 (4.2)	41 (6.5)	40 (7.0)	0.61 (0.37 – 0.99)	0.044	0.95 (0.62 – 1.48)	0.83
Other	**91 (14.8)**	**74 (11.7)**	**83 (14.3)**	**1.04 (0.77 – 1.40)**	**0.79**	**0.82 (0.60 – 1.13)**	**0.22**
Severe	21 (3.4)	23 (3.7)	23 (4.0)	0.86 (0.48 – 1.55)	0.62	0.92 (0.52 – 1.64)	0.78
Moderate	60 (9.9)	42 (6.8)	51 (8.8)	1.11 (0.77 – 1.62)	0.58	0.76 (0.51 – 1.15)	0.19
Mild	27 (4.5)	13 (2.1)	13 (2.3)	1.96 (1.01 – 3.80)	0.042	0.93 (0.43 – 2.00)	0.85

Note: Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Note: Event rate of first rehospitalization up to 360 days of study duration is calculated by the Kaplan-Meier method.
Note: Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Note: Rehospitalization is defined as the hospital admission after the first index event.
Note: Log-rank P-values as compared to VKA group are based on the two-sided log-rank test.
Note: An assessment of severity grade will be made using the following general categorical descriptors: a) *Mild*: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities; b) *Moderate*: Sufficient discomfort is present to cause interference with normal activity; c) *Severe*: Extreme distress, causing significant impairment of functioning or incapacitation and preventing normal everyday activities.

Table S4: Power calculation assuming a risk reduction of ≥ 20 % at a two-sided significance level of 0.05

Current Substudy			Main Study		
Endpoint	**Event rate**	**Power**	**Endpoint**	**Event rate**	**Power**
Overall					
Death or rehospitalization	41.9%	90.0%	Adverse CV event	6.0%	16.8%
Death or bleeding / cardiovascular rehosp.	36.4%	82.8%			
DAPT 1 month					
Death or rehospitalization	51.2%	97.1%	Adverse CV event	5.1%	14.9%
Death or bleeding / cardiovascular rehosp.	42.6%	90.7%			
DAPT 6 months					
Death or rehospitalization	42.7%	90.8%	Adverse CV event	4.3%	13.3%
Death or bleeding / cardiovascular rehosp.	38.6%	85.9%			
DAPT 12 months					
Death or rehospitalization	38.2%	85.4%	Adverse CV event	7.4%	19.9%
Death or bleeding / cardiovascular rehosp.	32.8%	76.8%			

Note: Power was calculated based on the observed event rate in the VKA arm using the Pearson's chi-square test.
Note: Both the treatment and control arms are standardized to 700 subjects.

Table S5: Baseline Characteristics by DAPT Stratum for Subjects (Group 2 or Group 3)

Characteristic	DAPT 1 Month (N = 224)	DAPT 6 Months (N = 494)	DAPT 12 Months (N = 697)	p-value
Demographics				
Age				
Mean ─ yr	71.7 ± 8.7	69.9 ± 8.7	69.4 ± 9.0	0.003
≥ 65 yr ─ no. (%)	176 (78.6)	368 (74.5)	498 (71.5)	0.095
≥ 75 yr ─ no. (%)	95 (42.4)	163 (33.0)	217 (31.1)	0.008
Female sex ─ no. (%)	48 (21.4)	127 (25.7)	187 (26.8)	0.272
Race*─ no. (%)				0.172
White	216 (96.4)	457 (92.5)	662 (95.0)	
Black or African-American	1 (0.5)	1 (0.2)	2 (0.3)	
Asian	5 (2.2)	31 (6.3)	25 (3.6)	
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	
Other or unknown	2 (0.9)	5 (1.0)	8 (1.2)	
BMI†				
Median	27.8	29.1	28.6	0.259
Interquartile range	25.4 – 32.5	25.8 – 32.6	25.8 – 32.4	
Active smokers – no. (%)	13 (5.8)	37 (7.5)	54 (7.8)	0.618
Creatinine clearance ─ ml/min‡				
Mean	75.9 ± 33.4	79.6 ± 29.8	79.8 ± 30.9	0.255
< 60 to ≥ 30 ml/min ─ no. (%)	68 (31.9)	138 (28.9)	165 (25.1)	0.104
<30 ml/min ─ no. (%)	2 (0.9)	1 (0.2)	6 (0.9)	0.276
P2Y12 inhibitor at baseline – no. (%)				0.056
Clopidogrel	221 (98.7)	467 (94.5)	656 (94.1)	
Prasugrel	1 (0.5)	4 (0.8)	11 (1.6)	
Ticagrelor	2 (0.9)	23 (4.7)	30 (4.3)	
Index Event				
Type of Index Event – no. (%)				0.089
NSTEMI	28 (12.8)	96 (19.6)	128 (18.6)	
STEMI	18 (8.3)	65 (13.3)	88 (12.8)	
Unstable Angina	53 (24.3)	107 (21.9)	152 (22.1)	
Stable Angina	119 (54.6)	221 (45.2)	319 (46.4)	
Type of Stent – no. (%)				<0.001
Drug-eluting stent	67 (29.9)	374 (75.9)	498 (72.0)	
Bare metal stent	156 (69.6)	114 (23.1)	174 (25.1)	
Drug-eluting and bare metal stents	1 (0.5)	5 (1.0)	20 (2.9)	
Urgency of Revascularization – no. (%)				<0.001
Elective	157 (70.1)	324 (65.6)	398 (57.1)	
Urgent	67 (29.9)	170 (34.4)	299 (42.9)	
Type of Atrial Fibrillation ─ no. (%)				0.037

Characteristic	DAPT 1 Month (N = 224)	DAPT 6 Months (N = 494)	DAPT 12 Months (N = 697)	p-value
Persistent	52 (23.2)	121 (24.5)	122 (17.5)	
Permanent	78 (34.8)	154 (31.2)	249 (35.8)	
Paroxysmal	94 (42.0)	219 (44.3)	325 (46.7)	
Bleed Risk Scores				
$CHADS_2$ risk of stroke – no. (%)				0.270
0	28 (12.5)	53 (10.7)	92 (13.2)	
1	74 (33.0)	147 (29.8)	238 (34.2)	
2	82 (36.6)	204 (41.3)	243 (34.9)	
3	32 (14.3)	81 (16.4)	112 (16.1)	
4	8 (27.6)	9 (1.8)	12 (1.7)	
5	0 (0.0)	0 (0.0)	0 (0.0)	
6	0 (0.0)	0 (0.0)	0 (0.0)	
CHA_2DS_2-VASc risk of stroke – no. (%)				0.457
0	3 (1.3)	4 (0.8)	10 (1.4)	
1	16 (7.1)	32 (6.5)	61 (8.8)	
2	34 (15.2)	55 (11.1)	100 (14.4)	
3	45 (20.1)	92 (18.6)	133 (19.1)	
4	48 (21.4)	121 (24.5)	158 (22.7)	
5	43 (19.2)	103 (20.9)	142 (20.4)	
6	32 (14.3)	72 (14.6)	72 (10.3)	
7	3 (1.3)	15 (3.0)	21 (3.0)	
HAS Bled Score – no. (%)				0.031
0	0 (0.0)	1 (0.2)	1 (0.1)	
1	8 (3.6)	15 (3.0)	46 (6.6)	
2	46 (20.5)	128 (25.9)	190 (27.3)	
3	103 (46.0)	200 (40.5)	299 (42.9)	
4	54 (24.1)	122 (24.7)	138 (19.8)	
5	13 (5.8)	27 (5.5)	21 (3.0)	
6	0 (0.0)	1 (0.2)	2 (0.3)	
Comorbidities				
Congestive heart failure	46 (20.5)	135 (27.3)	181 (26.0)	0.147
Hypertension	165 (73.7)	508 (72.9)	378 (76.5)	0.359
Diabetes mellitus	60 (26.8)	158 (32.0)	202 (29.0)	0.314
Hypercholesterolemia	97 (43.3)	225 (45.6)	289 (41.5)	0.374
Previous myocardial infarction	47 (21.0)	111 (22.5)	179 (25.7)	0.244
Peripheral vascular disease	11 (4.9)	27 (5.5)	39 (5.6)	0.925
Gastrointestinal bleeding	1 (0.5)	4 (0.8)	9 (1.3)	0.620
Medications				
Aspirin[¥]	222 (99.1)	493 (99.8)	695 (99.7)	0.309
Beta-blocker	175 (78.1)	375 (75.9)	528 (75.8)	0.757
ACE inhibitor or ARB	168 (75.0)	385 (77.9)	516 (74.0)	0.297

Characteristic	DAPT 1 Month (N = 224)	DAPT 6 Months (N = 494)	DAPT 12 Months (N = 697)	p-value
Statin	164 (73.2)	374 (75.7)	571 (81.9)	0.005
Proton pump inhibitor				0.406
Omeprazole or esomeprazole	27 (12.1)	53 (10.7)	77 (11.1)	
Other	59 (26.3)	118 (23.9)	200 (28.7)	

*Race was self-reported.
† Body mass index (BMI) is the weight (kg) divided by the square of the height (m).
‡ Creatinine clearance calculated using the Cockcroft-Gault equation.
¥ Aspirin use was calculated as administration of aspirin no more than 4 days after PCI procedure for index event.
Note: Plus-minus values are mean ± SD. ACE denotes angiotensin-converting enzyme, ACS acute coronary syndrome, ARB angiotensin-receptor blocker, BMI denotes body mass index, PCI percutaneous coronary intervention, NSTEMI non-ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction.
Note: Numbers based upon all randomized subjects.
Note: Comparisons were calculated using the chi-square test of independence for categorical variables, ANOVA for parametric continuous variables, and Wilcoxon rank sum test for non-parametric continuous variables.

Table S6: Baseline Characteristics by DAPT Duration (1 month) and Treatment

Characteristic	Group 2 Rivaroxaban + DAPT (N = 109)	Group 3 VKA + DAPT (N = 115)	p-value
Demographics			
Age			
Mean ─ yr	70.8 ± 9.6	72.6 ± 7.8	0.126
≥ 65 yr ─ no. (%)	80 (73.4)	96 (83.5)	0.066
≥ 75 yr ─ no. (%)	44 (40.4)	51 (44.4)	0.547
Female sex ─ no. (%)	24 (22.0)	24 (20.9)	0.834
Race*─ no. (%)			0.791
White	105 (96.3)	111 (96.5)	
Black or African-American	0 (0.0)	1 (0.9)	
Asian	2 (1.8)	3 (2.6)	
American Indian or Alaska Native	0 (0.0)	0 (0.0)	
Other or unknown	2 (1.8)	0 (0.0)	
BMI†			
Median	27.8	27.7	0.654
Interquartile range	25.5 – 33.2	25.4 – 32.0	
Active smokers – no. (%)	5 (4.6)	8 (7.0)	0.448
Creatinine clearance ─ ml/min‡			
Mean	78.3 ± 37.1	73.5 ± 29.3	0.302
< 60 to ≥ 30 ml/min ─ no. (%)	28 (26.7)	40 (37.0)	0.105
<30 ml/min ─ no. (%)	2 (1.9)	0 (0.0)	0.242
P2Y12 inhibitor at baseline – no. (%)			0.236
Clopidogrel	107 (98.2)	114 (99.1)	
Prasugrel	0 (0.0)	1 (0.9)	
Ticagrelor	2 (1.8)	0 (0.0)	
Index Event			
Type of Index Event – no. (%)			0.385
NSTEMI	16 (14.8)	12 (10.9)	
STEMI	9 (8.3)	9 (8.2)	
Unstable Angina	21 (19.4)	32 (29.1)	
Stable Angina	62 (57.4)	57 (51.8)	
Type of Stent – no. (%)			0.611
Drug-eluting stent	34 (31.2)	33 (28.7)	
Bare metal stent	74 (67.9)	82 (71.3)	
Drug-eluting and bare metal stents	1 (0.9)	0 (0.0)	
Urgency of Revascularization – no. (%)			0.908
Elective	76 (69.7)	81 (70.4)	
Urgent	33 (30.3)	34 (29.6)	
Type of Atrial Fibrillation ─ no. (%)			0.176

Characteristic	Group 2 Rivaroxaban + DAPT (N = 109)	Group 3 VKA + DAPT (N = 115)	p-value
Persistent	20 (18.4)	32 (27.8)	
Permanent	43 (39.5)	35 (30.4)	
Paroxysmal	46 (42.2)	48 (41.7)	
Bleed Risk Scores			
$CHADS_2$ risk of stroke – no. (%)			0.184
0	16 (14.7)	12 (10.4)	
1	39 (35.8)	35 (30.4)	
2	32 (29.4)	50 (43.5)	
3	19 (17.4)	13 (11.3)	
4	3 (2.8)	5 (4.4)	
5	0 (0.0)	0 (0.0)	
6	0 (0.0)	0 (0.0)	
CHA_2DS_2-VASc risk of stroke – no. (%)			0.180
0	2 (1.8)	1 (0.9)	
1	12 (11.0)	4 (3.5)	
2	13 (11.9)	21 (18.3)	
3	19 (17.4)	26 (22.6)	
4	20 (18.4)	28 (24.4)	
5	23 (21.1)	20 (17.4)	
6	19 (17.4)	13 (11.3)	
7	1 (0.9)	2 (1.7)	
HAS Bled Score – no. (%)			0.671
0	0 (0.0)	0 (0.0)	
1	5 (4.6)	3 (2.6)	
2	23 (21.1)	23 (20.0)	
3	45 (41.3)	58 (50.4)	
4	29 (26.6)	25 (21.7)	
5	7 (6.4)	6 (5.2)	
6	0 (0.0)	0 (0.0)	
Comorbidities			
Congestive heart failure	21 (19.3)	25 (21.7)	0.647
Hypertension	77 (70.6)	88 (76.5)	0.318
Diabetes mellitus	30 (27.5)	30 (26.1)	0.808
Hypercholesterolemia	38 (34.9)	59 (51.3)	0.013
Previous myocardial infarction	19 (17.4)	28 (24.4)	0.204
Peripheral vascular disease	7 (6.4)	4 (3.5)	0.308
Gastrointestinal bleeding	0 (0.0)	1 (0.9)	>0.999
Medications			
Aspirin[¥]	108 (99.1)	114 (99.1)	>0.999
Beta-blocker	87 (79.8)	88 (76.5)	0.551
ACE inhibitor or ARB	83 (76.2)	85 (73.9)	0.700

Characteristic	Group 2 Rivaroxaban + DAPT (N = 109)	Group 3 VKA + DAPT (N = 115)	p-value
Statin	79 (72.5)	85 (73.9)	0.808
Proton pump inhibitor			0.107
Omeprazole or esomeprazole	9 (8.3)	18 (15.7)	
Other	34 (31.2)	25 (21.7)	

*Race was self-reported.
† Body mass index (BMI) is the weight (kg) divided by the square of the height (m).
‡ Creatinine clearance calculated using the Cockcroft-Gault equation.
¥ Aspirin use was calculated as administration of aspirin no more than 4 days after PCI procedure for index event.
Note: Plus-minus values are mean ± SD. ACE denotes angiotensin-converting enzyme, ACS acute coronary syndrome, ARB angiotensin-receptor blocker, BMI denotes body mass index, PCI percutaneous coronary intervention, NSTEMI non-ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction.
Note: Numbers based upon all randomized subjects and available data.
Note: Pairwise comparisons were calculated using the chi-square test of independence for categorical variables, independent samples t-test for parametric continuous variables, and Wilcoxon rank sum test for non-parametric continuous variables.

Table S7: Baseline Characteristics by DAPT Duration (6 months) and Treatment

Characteristic	**Group 2** Rivaroxaban + DAPT (N = 248)	**Group 3** VKA + DAPT (N = 246)	**p-value**
Demographics			
Age			
Mean ─ yr	70.2 ± 9.1	69.6 ± 8.3	0.403
≥ 65 yr ─ no. (%)	183 (73.8)	185 (75.2)	0.719
≥ 75 yr ─ no. (%)	90 (36.3)	73 (29.7)	0.118
Female sex ─ no. (%)	65 (26.2)	62 (25.2)	0.798
Race*─ no. (%)			0.039
White	235 (94.8)	222 (90.2)	
Black or African-American	1 (0.4)	0 (0.0)	
Asian	11 (4.4)	20 (8.1)	
American Indian or Alaska Native	0 (0.0)	0 (0.0)	
Other or unknown	1 (0.4)	4 (1.6)	
BMI†			
Median	28.7	29.4	0.297
Interquartile range	25.7 – 32.3	25.8 – 32.8	
Active smokers – no. (%)	21 (8.5)	16 (6.5)	0.407
Creatinine clearance ─ ml/min‡			
Mean	77.5 ± 30.0	81.8 ± 29.5	0.114
< 60 to ≥ 30 ml/min ─ no. (%)	78 (32.2)	60 (25.5)	0.108
<30 ml/min ─ no. (%)	1 (0.4)	0 (0.0)	>0.999
$P2Y_{12}$ inhibitor at baseline – no. (%)			0.370
Clopidogrel	231 (93.2)	236 (95.9)	
Prasugrel	3 (1.2)	1 (0.4)	
Ticagrelor	14 (5.7)	9 (3.7)	
Index Event			
Type of Index Event – no. (%)			0.451
NSTEMI	51 (20.7)	45 (18.5)	
STEMI	38 (15.5)	27 (11.1)	
Unstable Angina	52 (21.1)	55 (22.6)	
Stable Angina	105 (42.7)	116 (47.7)	
Type of Stent – no. (%)			0.509
Drug-eluting stent	187 (75.7)	187 (76.0)	
Bare metal stent	56 (22.7)	58 (23.6)	
Drug-eluting and bare metal stents	4 (1.6)	1 (0.4)	
Urgency of Revascularization – no. (%)			0.101
Elective	154 (62.1)	170 (69.1)	
Urgent	94 (37.9)	76 (30.9)	

Characteristic	Group 2 Rivaroxaban + DAPT (N = 248)	Group 3 VKA + DAPT (N = 246)	p-value
Type of Atrial Fibrillation ─ no. (%)			0.932
Persistent	60 (24.2)	61 (24.8)	
Permanent	76 (30.7)	78 (31.7)	
Paroxysmal	112 (45.2)	107 (43.5)	
Bleed Risk Scores			
$CHADS_2$ risk of stroke – no. (%)			0.676
0	26 (10.5)	27 (11.0)	
1	74 (29.8)	73 (29.7)	
2	108 (43.6)	96 (39.0)	
3	35 (14.1)	46 (18.7)	
4	5 (2.0)	4 (1.6)	
5	0	0	
6	0	0	
CHA_2DS_2-VASc risk of stroke – no. (%)			0.381
0	2 (0.8)	2 (0.8)	
1	20 (8.1)	12 (4.9)	
2	24 (9.7)	31 (12.6)	
3	51 (20.6)	41 (16.7)	
4	55 (22.2)	66 (26.8)	
5	56 (22.6)	47 (19.1)	
6	35 (14.1)	37 (15.0)	
7	5 (2.0)	10 (4.1)	
HAS Bled Score – no. (%)			0.673
0	1 (0.4)	0 (0.0)	
1	10 (4.0)	5 (2.0)	
2	64 (25.8)	64 (26.0)	
3	100 (40.3)	100 (40.7)	
4	60 (24.2)	62 (25.2)	
5	12 (4.8)	15 (6.1)	
6	1 (0.4)	0 (0.0)	
Comorbidities			
Congestive heart failure	67 (27.0)	68 (27.6)	0.876
Hypertension	188 (75.8)	190 (77.2)	0.708
Diabetes mellitus	70 (28.2)	88 (35.8)	0.072
Hypercholesterolemia	109 (44.0)	116 (47.2)	0.475
Previous myocardial infarction	62 (25.0)	49 (19.9)	0.176
Peripheral vascular disease	12 (4.8)	15 (6.1)	0.538
Gastrointestinal bleeding	2 (0.8)	2 (0.8)	>0.999
Medications			
Aspirin[¥]	248 (100.0)	245 (99.6)	0.498
Beta-blocker	193 (77.8)	182 (74.0)	0.319

Characteristic	Group 2 Rivaroxaban + DAPT (N = 248)	Group 3 VKA + DAPT (N = 246)	p-value
ACE inhibitor or ARB	199 (80.2)	186 (75.6)	0.215
Statin	194 (78.2)	180 (73.2)	0.190
Proton pump inhibitor			0.108
Omeprazole or esomeprazole	30 (12.1)	23 (9.4)	
Other	67 (27.0)	51 (20.7)	

*Race was self-reported.
† Body mass index (BMI) is the weight (kg) divided by the square of the height (m).
‡ Creatinine clearance calculated using the Cockcroft-Gault equation.
¥ Aspirin use was calculated as administration of aspirin no more than 4 days after PCI procedure for index event.
Note: Plus-minus values are mean ± SD. ACE denotes angiotensin-converting enzyme, ACS acute coronary syndrome, ARB angiotensin-receptor blocker, BMI denotes body mass index, PCI percutaneous coronary intervention, NSTEMI non-ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction.
Note: Numbers based upon all randomized subjects and available data.
Note: Pairwise comparisons were calculated using the chi-square test of independence for categorical variables, independent samples t-test for parametric continuous variables, and Wilcoxon rank sum test for non-parametric continuous variables.

Table S8: Baseline Characteristics by DAPT Duration (12 months) and Treatment

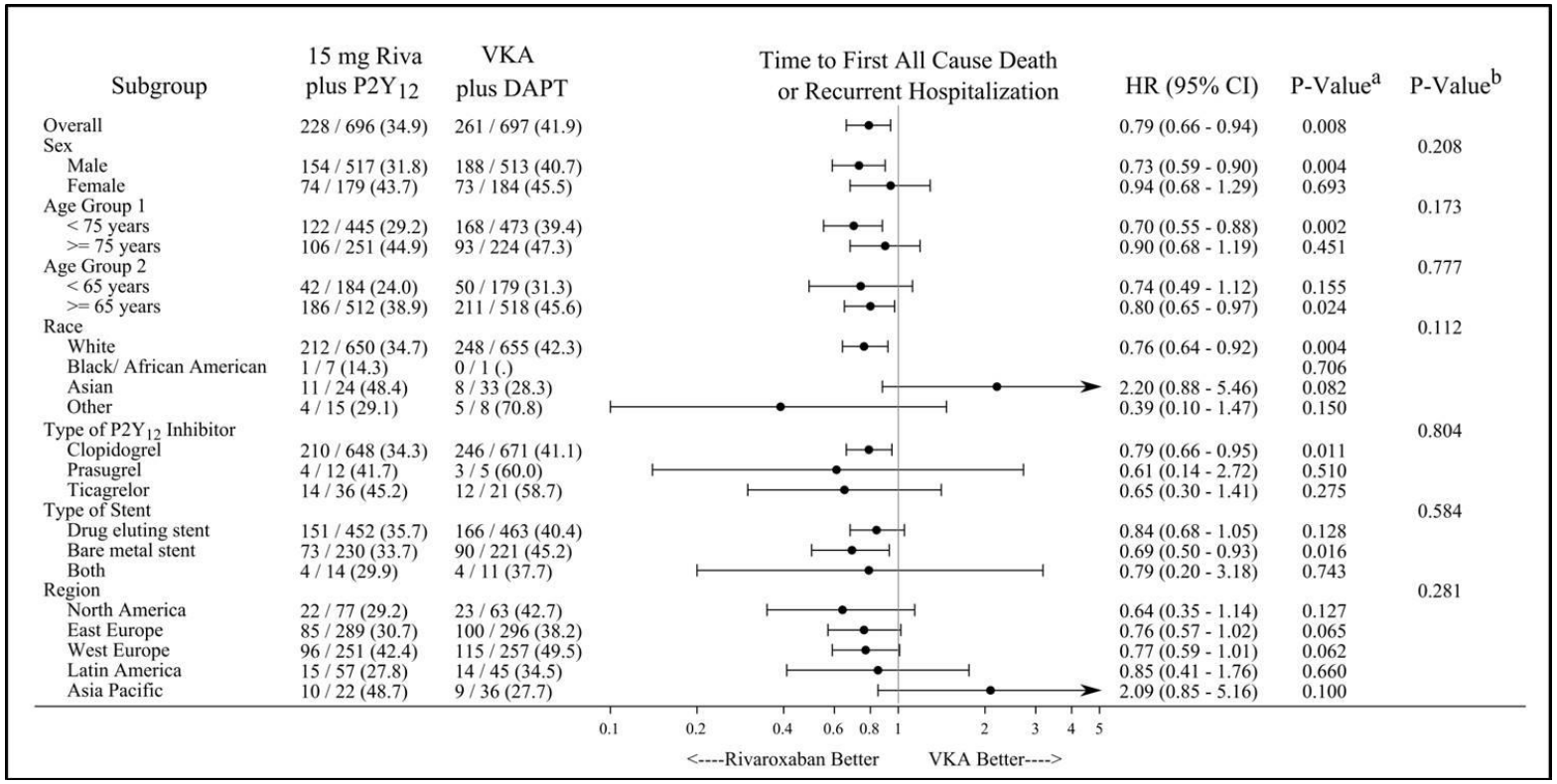
Characteristic	**Group 2** Rivaroxaban + DAPT (N = 352)	**Group 3** VKA + DAPT (N = 345)	**p-value**
Demographics			
Age			
Mean ─ yr	69.5 ± 9.0	69.3 ± 9.1	0.721
≥ 65 yr ─ no. (%)	253 (71.9)	245 (71.0)	0.801
≥ 75 yr ─ no. (%)	111 (31.5)	106 (30.7)	0.818
Female sex ─ no. (%)	85 (24.2)	102 (29.6)	0.107
Race*─ no. (%)			0.256
White	331 (94.0)	331 (95.9)	
Black or African-American	2 (0.6)	0 (0.0)	
Asian	15 (4.3)	10 (2.9)	
American Indian or Alaska Native	0 (0.0)	0 (0.0)	
Other or unknown	4 (1.1)	4 (1.2)	
BMI†			
Median	28.4	29.1	**0.035**
Interquartile range	25.6 – 31.6	26.1 – 32.9	
Active smokers – no. (%)	30 (8.5)	24 (7.0)	0.480
Creatinine clearance ─ ml/min‡			
Mean	77.3 ± 31.4	82.3 ± 30.3	**0.037**
< 60 to ≥ 30 ml/min ─ no. (%)	90 (27.0)	75 (23.1)	0.280
<30 ml/min ─ no. (%)	4 (1.2)	2 (0.6)	0.686
$P2Y_{12}$ inhibitor at baseline – no. (%)			0.180
Clopidogrel	326 (92.6)	330 (95.7)	
Prasugrel	8 (2.3)	3 (0.9)	
Ticagrelor	18 (5.1)	12 (3.5)	
Index Event			
Type of Index Event – no. (%)			0.639
NSTEMI	62 (17.8)	66 (19.5)	
STEMI	50 (14.3)	38 (11.2)	
Unstable Angina	75 (21.5)	77 (22.8)	
Stable Angina	162 (46.4)	157 (46.5)	
Type of Stent – no. (%)			0.834
Drug-eluting stent	250 (71.6)	248 (72.3)	
Bare metal stent	90 (25.8)	84 (24.5)	
Drug-eluting and bare metal stents	9 (2.6)	11 (3.2)	
Urgency of Revascularization – no. (%)			0.879
Elective	200 (56.8)	198 (57.4)	
Urgent	152 (43.2)	147 (42.6)	
Type of Atrial Fibrillation ─ no. (%)			0.481

Characteristic	Group 2 Rivaroxaban + DAPT (N = 352)	Group 3 VKA + DAPT (N = 345)	p-value
Persistent	66 (18.8)	56 (16.3)	
Permanent	119 (33.8)	130 (37.8)	
Paroxysmal	167 (47.4)	158 (45.9)	
Bleed Risk Scores			
$CHADS_2$ risk of stroke – no. (%)			0.522
0	48 (13.6)	44 (12.8)	
1	119 (33.8)	119 (34.5)	
2	116 (33.0)	127 (36.8)	
3	64 (18.2)	48 (13.9)	
4	5 (1.4)	7 (2.0)	
5	0	0	
6	0	0	
CHA_2DS_2-VASc risk of stroke – no. (%)			0.035
0	6 (1.7)	4 (1.2)	
1	33 (9.4)	28 (8.1)	
2	56 (15.9)	44 (12.8)	
3	52 (14.8)	81 (23.5)	
4	78 (22.2)	80 (23.2)	
5	84 (23.9)	58 (16.8)	
6	31 (8.8)	41 (11.9)	
7	12 (3.4)	9 (2.6)	
HAS Bled Score – no. (%)			0.520
0	1 (0.3)	0 (0.0)	
1	28 (8.0)	18 (5.2)	
2	95 (27.0)	95 (27.5)	
3	149 (42.3)	150 (43.5)	
4	68 (19.3)	70 (20.3)	
5	11 (3.1)	10 (2.9)	
6	0 (0.0)	2 (0.6)	
Comorbidities			
Congestive heart failure	99 (28.1)	82 (23.8)	0.190
Hypertension	254 (72.2)	254 (73.6)	0.664
Diabetes mellitus	99 (28.1)	103 (29.9)	0.615
Hypercholesterolemia	148 (42.1)	141 (40.9)	0.753
Previous myocardial infarction	99 (28.1)	80 (23.2)	0.136
Peripheral vascular disease	23 (6.5)	16 (4.6)	0.276
Gastrointestinal bleeding	7 (2.0)	2 (0.6)	0.177
Medications			
Aspirin[¥]	351 (99.7)	344 (99.7)	>0.999
Beta-blocker	261 (74.2)	267 (77.4)	0.318
ACE inhibitor or ARB	250 (71.0)	266 (77.1)	0.067

Characteristic	Group 2 Rivaroxaban + DAPT (N = 352)	Group 3 VKA + DAPT (N = 345)	p-value
Statin	284 (80.7)	287 (83.2)	0.390
Proton pump inhibitor			0.792
Omeprazole or esomeprazole	39 (11.1)	38 (11.0)	
Other	97 (27.6)	103 (29.9)	

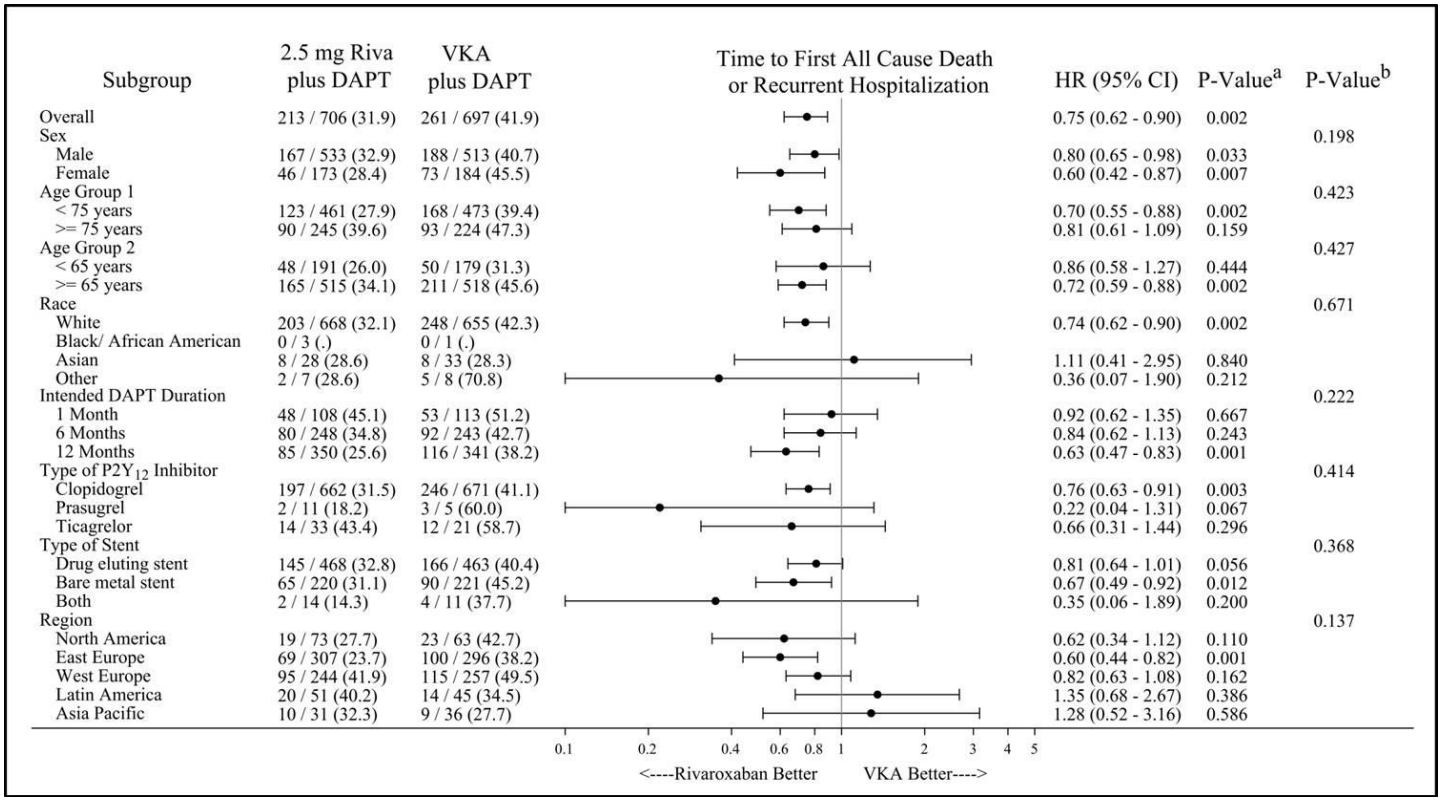
*Race was self-reported.
† Body mass index (BMI) is the weight (kg) divided by the square of the height (m).
‡ Creatinine clearance calculated using the Cockcroft-Gault equation.
¥ Aspirin use was calculated as administration of aspirin no more than 4 days after PCI procedure for index event.
Note: Plus-minus values are mean ± SD. ACE denotes angiotensin-converting enzyme, ACS acute coronary syndrome, ARB angiotensin-receptor blocker, BMI denotes body mass index, PCI percutaneous coronary intervention, NSTEMI non-ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction.
Note: Numbers based upon all randomized subjects.
Note: Pairwise comparisons were calculated using the chi-square test of independence for categorical variables, independent samples t-test for parametric continuous variables, and Wilcoxon rank sum test for non-parametric continuous variables.

Figure S1: Subgroup Analysis of All-Cause Death or First Recurrent Hospitalization 15 mg Rivaroxaban plus $P2Y_{12}$ Inhibitors vs. VKA plus DAPT



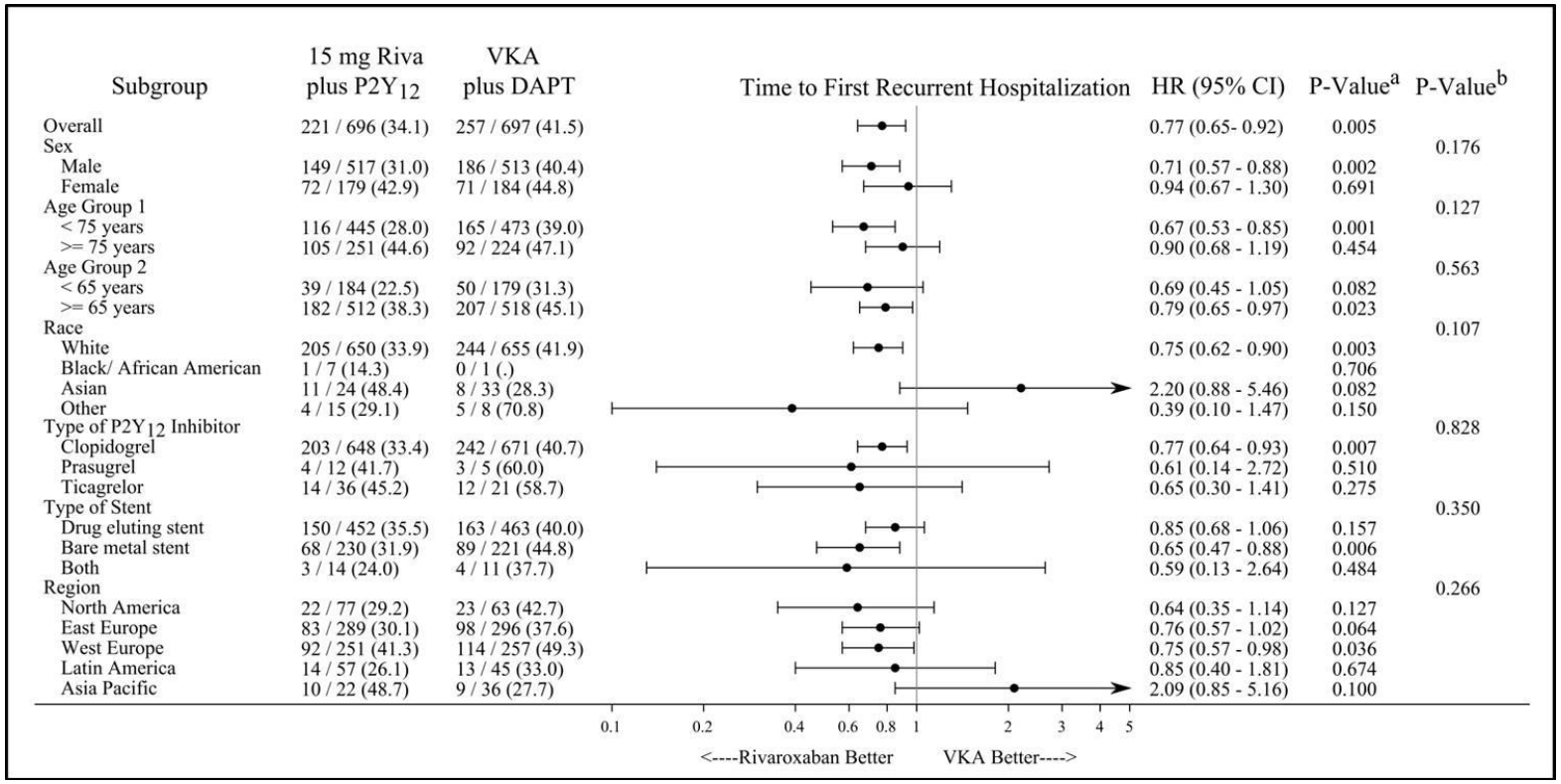
Note: Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Note: KM Estimate represents rate of first re-hospitalization from treatment start date to 360 days of study direction.
Note: A subject could have more than one component event. n = number of subjects with events, N = number of subjects at risk.
Note: Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.
Note: Rehospitalizations do not include first index event hospitalization.
[a]Log-Rank p-values as compared to VKA group are based on the two-sided log rank test.
[b] P-Value for Interaction based on the Cox proportional Hazard joint test. References for joint test are as follow; Sex; male; Age Group 1: < 75 years; Age Group 2: < 65 years; Race: White; Type of $P2Y_{12}$ inhibitor: Clopidogrel; Type of Stent; Drug Eluting Stent; Region: North America.

Figure S2: Subgroup Analysis of All Cause Death or First Recurrent Hospitalization 2.5 mg Rivaroxaban plus DAPT vs. VKA plus DAPT



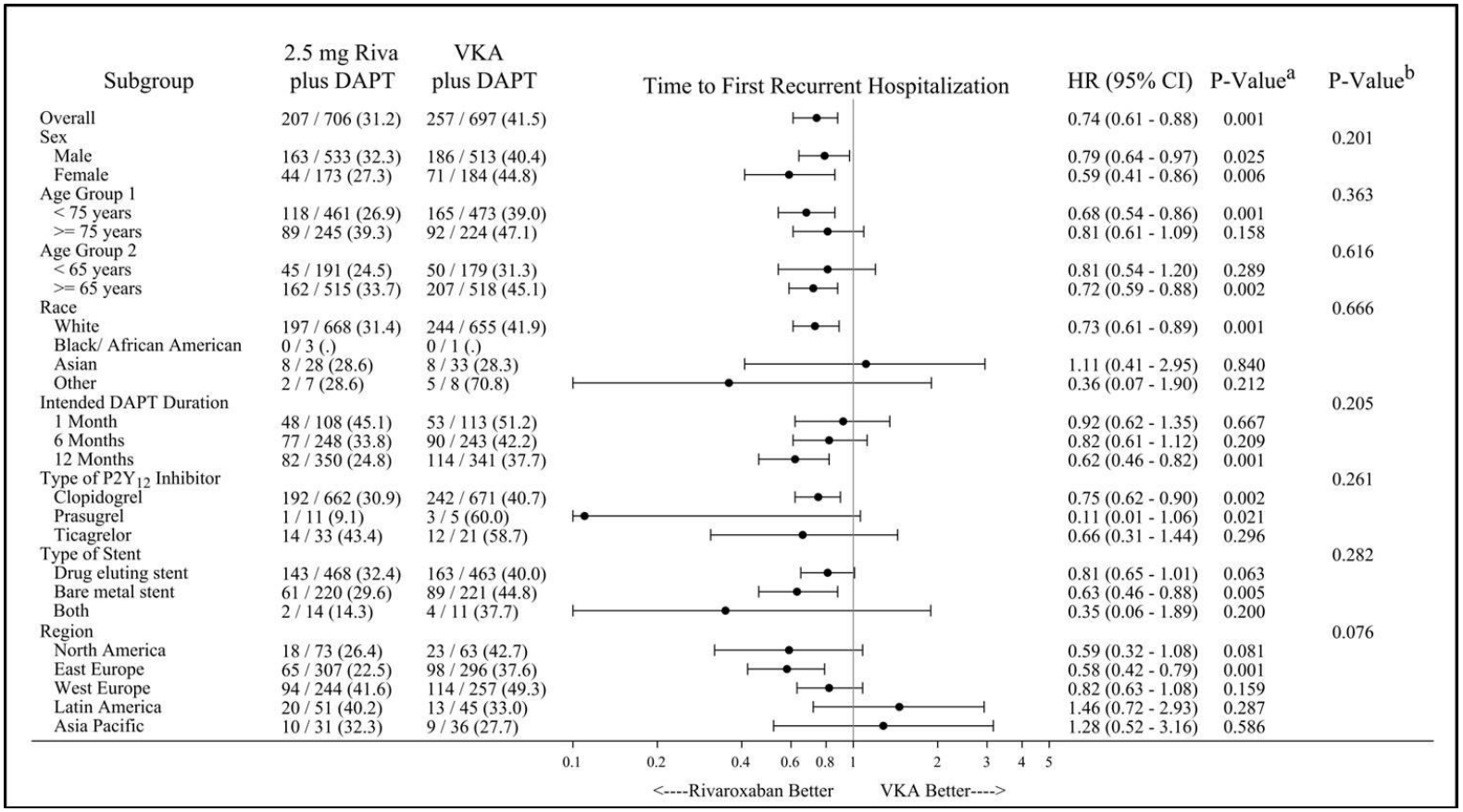
Note: Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Note: KM Estimate represents rate of first re-hospitalization from treatment start date to 360 days of study direction.
Note: A subject could have more than one component event. n = number of subjects with events, N = number of subjects at risk.
Note: Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.
Note: Rehospitalizations do not include first index event hospitalization.
[a]Log-Rank p-values as compared to VKA group are based on the two-sided log rank test.
[b] P-Value for Interaction based on the Cox proportional Hazard joint test. References for joint test are as follow; Sex; male; Age Group 1: < 75 years; Age Group 2: < 65 years; Race: White; Intended DAPT Duration: 1 Month; Type of $P2Y_{12}$ inhibitor: Clopidogrel; Type of Stent; Drug Eluting Stent; Region: North America.

Figure S3: Subgroup Analysis of First Recurrent Hospitalization 15 mg Rivaroxaban plus $P2Y_{12}$ Inhibitors vs. VKA plus DAPT



Note: Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Note: KM Estimate represents rate of first re-hospitalization from treatment start date to 360 days of study direction.
Note: A subject could have more than one component event. n = number of subjects with events, N = number of subjects at risk.
Note: Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.
Note: Rehospitalizations do not include first index event hospitalization.
[a]Log-Rank p-values as compared to VKA group are based on the two-sided log rank test.
[b] P-Value for Interaction based on the Cox proportional Hazard joint test. References for joint test are as follow; Sex; male; Age Group 1: < 75 years; Age Group 2: < 65 years; Race: White; Type of $P2Y_{12}$ inhibitor: Clopidogrel; Type of Stent; Drug Eluting Stent; Region: North America.

Figure S4: Subgroup Analysis of First Recurrent Hospitalization
2.5 mg Rivaroxaban plus DAPT vs. VKA plus DAPT



Note: Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Note: KM Estimate represents rate of first re-hospitalization from treatment start date to 360 days of study direction.
Note: A subject could have more than one component event. n = number of subjects with events, N = number of subjects at risk.
Note: Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.
Note: Rehospitalizations do not include first index event hospitalization.

[a]Log-Rank p-values as compared to VKA group are based on the two-sided log rank test.
[b] P-Value for Interaction based on the Cox proportional Hazard joint test. References for joint test are as follow; Sex; male; Age Group 1: < 75 years; Age Group 2: < 65 years; Race: White; Intended DAPT Duration: 1 Month; Type of $P2Y_{12}$ inhibitor: Clopidogrel; Type of Stent; Drug Eluting Stent; Region: North America.